Remarks / Reply to 2nd office action and phone interview begins on Page 5 of this paper, and includes new information (from prior art) on supporting the patentability of our method for cognitive distortion. The reply continues (page 6) to answer the new line of reasoning brought up by the PTO on Faour's prior art at the time of the phone interview. Further notes on the phone interview begin at page 15. Continuation of the Reply to the 2nd OA follows on page 16, (alternate claim language for discussion is at pages 40-42), and the continuation of the reply is continued with a detailed "**line-by-line-reply**" on Page 46 (and follows literally a line-by-line reply to the examiner's arguments). **Discussion of Information Disclosure** is at pages 80-82, and 83-85.

Discussion in light of prior art of the **new claims with atypical antipsychotic monotherapy** begins at page 83.

Claims discussion/Summary of the reply to the Claim Objections begins at page 86.

Summary and Conclusions begin on Page 130.

The previous reply to the 1st OA is maintained, and is incorporated explicitly herein for reference, (to avoid unnecessary repetition). It is respectfully submitted that the PTO's response to our reply to the 1st OA was often generalized, leaving out important parts unanswered, and disregarding important facts (like the secondary factors, our theory and reasons for how our methods would work) or many explanations that we have numbered [like on cognitive distortion].

The length of this and the prior reply was necessitated by a) because the examiners are not clinicians and the PTO's thinking pattern in both actions deviated so much from the standard of care, and b) because the PTO has repeated itself, and c) because the PTO has presented an unconvincing line of reasoning on a number of occasions (even with their tenets not being substantiated by facts), and d) because the PTO disregarded relevant parts from the 1st OA or from the prior submitted applications.

Applicant also includes **enclosures**, and **attachments** (copies of selected – relevant – professional publications or patents referenced in the reply – and that also includes a list of **Secondary factors in determining unobviousness from a patent book,** since the secondary factors were left out of consideration in our reply to the 1st OA.), **Form RCE, Information disclosure form** (for literature and patents – with enclosed copies for all except PTO publication), **request of three months extension of time, check** for payment. (The IACtr/PTO [ref# 193310452 and 193756046] has assisted the applicant to calculate fees and put applicant on hold to double check that indeed fees are due only for new and not the amended claims with the RCE).

In addition, please note that the **Applicant has lost his attorney representation, is relying on your guidance**, and that his best (timely) contact is through his cell phone **(724)840-0464** – specifically that he may need to go out of state for medical appointment(s), (therefore his mail may not be promptly accessible, if he does not know when it is coming).

Help request from the PTO examiner and Questions:

I would like to continue request help from the PTO including and as needed for claim-drafting assistance **under MPEP 707.07(j)** – (see also #14 at page 35). I'd like to do that not only in general, (as hopefully most of my claims would be in order), but **also** with special emphasis on checking the following:

1) The "**or**" is used in many of the claims, and I would like to be sure that it is not invalidating the claims. E.g.: "said treatment is given at a time selected from the group consisting of, as initial treatment **or** as soon as possible, **or** upon presentation to a physician **or** a health care provider". (Also I would like to be sure that the "given at a time" is clear and acceptable).
2) **Dash ("/")** had been used in some of the original and current claims: in Claim 1-3, 11, for example: (...combined action **SSRI/SNRI, serotonin-2 antagonist/reuptake** inhibitors, ...**serotonin/norepinephrine/dopamine** reuptake inhibition, ... **substance P antagonists/ neurokinin-1** receptor antagonists,...
3) I have noted that even when I had an attorney (and the claims were seen by PTO) many places the word "said" was missing or "the" was used instead [like antidepressant, instead of "said" antidepressant. That created misunderstanding in the case of "substantially of all of said patients". I have corrected these omissions, but at times I also changed the "the" to a "said"; and I would like to be sure that this is acceptable.
4) I'd like to ask you to make sure that no claims contain "means plus function" – as I read that this would not be permissible.

Alternate claim language – if the current amendment for claims 1-3 would not be acceptable after reading our reply – is listed at **page 40-42** after #6 (that was moved to before #17).

List of enclosed of patent documents and articles: (in addition to original provisional application with font size 14)

1a) Secondary factors in determining unobviousness. From Patent attorney David Pressman, Book: "Patent it yourself". Nolo, 2004 10th edition, pages 5/19- 5/22.

1b) General arguments against obviousness. From Patent attorney David Pressman, Book: "Patent it yourself". Nolo, 2004 10th edition, pages 13/25-13/16.

1c) A14 A request for claim-drafting assistance under MPEP 707.07(j) ... (Showing that the PTO has to give assistance in claim drafting – which is against the PTO statement in the interview. From Patent attorney David Pressman, Book: "Patent it yourself". Nolo, 2004 10th edition, pages 13/46.

5,958,921 (PTO) was referenced, but not enclosed as it is a PTO publication.

Appelberg B.G. at al. Patients with severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-bind, placebo wash-in study. J Clin Psychiatry. 2001 Jun; 62(6):448-52.

Beasely CM et al Olanzapine versus placebo and Haloperidol. Acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 14: 111-123 1996

Birmaher B et al Fluoxetine for childhood anxiety disorders. J. Am Acad. Child Adolesc. Psychiatry, 33:7 1994, 993-999

Business2 (page 64 March 2006) as referenced on page 39 #20).

Dunner DL. The issue of comorbidity in the treatment of panic. International Clinical Psychopharmacology 1998, Vol 13 (Suppl. 4) S19-24.

Evins at al. Buproprion and smoking cessation (Am. J. Psychiatry 156:5, May 1999 pages 798-799.)

FDA loosing credibility with public, own staff. Clinical Psychiatry News 34:12 December 2006, page 67 as referenced on page 35 ##14).

Goodnick PJ at al Mirtazapine in Major Depression With Comorbid Generalized Anxiety Disorder. J. Clin Psychiatry 1999, 60:7, 446-448,

Khan A et al Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. J Affect Disord, 2002 Apr; 68(2-3):183-90)

Miller I.W. et al Treatment response of high cognitive dysfunction depressed inpatients. Comprehensive psychiatry 1990 Vol. 30 (1) 62-71.

Nesbitt and Pharmacia & Upjohn company WO 02/053140 A2

Pertinent parts on depression from the **DSM-IV-TR**, as a reminder,

Ralph and Pfizer EP 1238676 A1.

Silverstone PH et al Efficacy of Venlafaxine Exended Release in patients with Major Depressive Disorder and Comorbid Generalized Anxiety disorder. J. Clin Psychiatry 2001 (July), 62:523-529,

Thase M.E. Treatment issues related to sleep and depression. J. Clin Psychiatry 2000; 61[suppl 11]:46-50.

Tiverdi MH et al Do buproprion SR and sertraline differ in their effects on anxiety in depressed patients? J. Clin Psychiatry 62:10 2001, 776-781.

Tollefson and Eli Lilly company EP 0966967 A2.

Tollefson and Eli Lilly company EP 0958824 A2.

Tollefson GD et al (1998a) Depressive signs and symptoms in Schizophrenia. A prospective blinded trial of olanzapine and haloperidol. Arch Gen Psychiatry 1998; 55:250-258.

Tollefson GD et al (1998b) A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998; 43:803-810.

Remarks / **Reply to 2nd office action and phone interview (that was following the 2nd OA):**

(2nd reply) On Cognitive distortion:

The PTO at page 27 of the 2nd Office Action (OA) rejected our claim of using our method for cognitive distortion with the non-convincing line of reasoning, that "One of ordinary skill in the art would have been motivated to use the method for treating cognitive distortions because cognitive distortions as defined by Applicant are often associated with depression." The applicant traverses that and is maintaining his argument at the 1st OA. Associative and causative factors are different as described in detail under Reply Q (q). Furthermore – as an analogy – just because a car can be propelled by gasoline, that does not mean that it cannot be propelled also by electricity in a hybrid car. Therefore specifically targeting cognitive distortion with our method is different from prior art and has added value. The applicant also traverses the PTO's unconvincing line of reasoning on the bases of additional information presented here:

The following publication is referenced herein: **Miller I.W. et al Treatment response of high cognitive dysfunction depressed inpatients. Comprehensive psychiatry 1990 Vol. 30 (1) 62-71.** This study demonstrated that patients with "high levels of cognitive dysfunction has persistent dysfunctional cognitions after remission of depressive symptoms". (page 63 lines 9-10). That is **after the treatment of depression** at least what is demonstrable in some of the patients at this sample size **the cognitive distortion remains**. Although the psychological tests used in this study is not in the arsenal of the average (and most) clinician/artisan, this study has the proof with statistical significance that the target treatment of depression does not equal with the target treatment of cognitive distortion. Moreover, that study shows, that the cognitive distortion after the remission of the depressive symptoms can be specifically targeted by other methods (here the cognitive therapy). For statistically significant differences often very large sample sizes would be required in the research studies as this had been specifically demonstrated in other aspects of the treatment of depression (e.g. in demonstrating of which antidepressant is more effective). Our various and detailed arguments in the reply to the 1st OA would make this data generally be true for depression. Therefore – even as is - that Miller reference is a proof that the PTO's statement that the treatment of depression would equal the treatment of cognitive distortion is incorrect (and an unconvincing line of reasoning). **Moreover, and most importantly**, this study showed that high cognitive dysfunction (HCD) subjects receiving combined treatment of pharmacotherapy and cognitive [talking] therapy had a higher percentage of response (over three times the response rate) than patients receiving pharmacotherapy alone. (page 69 lines 4-6). **That means – and that can be definitely generalized for all types of depression – that cognitive therapy or other treatment modalities – like our method - specifically targeting the cognitive distortion would have additional benefits just as a different fuel would have in a hybrid car.** That is clearly patentable and not the same as treating the depression with an antidepressant.
The remission of depressive symptom does not equal with the elimination of cognitive distortion. This is what we have also argued in the reply to the 1st OA. Therefore new methods like ours can provide further benefit and this is a solution for a long felt need – with added emphasis in case of resisting suicide – and that is patentable.

Therefore even with the strictest interpretation by the PTO, and in the worst scenario (if we could not defend the rest of our claims otherwise), our method and most of our claims for treating depression – through targeting the treatment of cognitive distortion – should be still allowable.

The PTO have failed to show any prior art that would describe and also enable that both antidepressants and the antipsychotic drugs specifically and as causative factor would target the cognitive distortions in

the depressed, **and** that indeed that this is the identified mechanism of action for both of these classes of medications. That information is clearly missing in prior art. Our invention is clearly distinguishable from prior art. [See also Reply Q (q)].

(2nd reply) New line of reasoning brought up by PTO at the phone interview on Faour – Reply to this segment of the phone interview. [The phone interview was only allowed after the 2nd Office Action (OA)].

At the phone interview the PTO junior examiner listened but did not withdraw any of the PTO viewpoints of the 1st or 2nd Office Action (OA) (stating that he is a junior examiner and is not allowed to do so). However the PTO listened to my reasoning, and reviewed Fig 1-3 that was faxed.
After listening to the applicant's "theory", - the existence of which was previously denied or subsequently find "not-relevant" in the prior OAs, - the PTO stated that "it seems that Faour was stating a similar explanation than you did about anxiety". The PTO at the interview stated that Faour's statement - as is - should be sufficient for enablement for Faour.
As for help, the PTO suggested that the applicant should exclude anxiety in depression in his claims but also added that even though in the provisional the applicant have noted that "it is known that antipsychotics are useful for the treatment of anxiety", that may be still considered by the PTO as a new matter if the applicant does the exclusions in the claims.

The applicant traverses the line of such reasoning being convincing, and most importantly even the need of such exclusions:

1) **–A)** It is known that the purpose of DSM is to offer guidelines for making diagnosis, and also because it has been demonstrated that the use of such criteria enhances the agreement among clinicians and investigators. Therefore the DSM makes it possible so that the artisans would mean the same thing when they communicate with each other. We have submitted copies of the pertinent parts on depression from the DSM-IV-TR, but as a reminder let's bring it up again that aside of the diagnostic criteria for depression (or Major Depressive disorder) the DSM also provides the following **specifyers**:
    a) Mild, Moderate, Severe Without Psychotic Features/ Severe With Psychotic Features
    b) Chronic
    c) With catatonic Features
    d) With atypical Features
    e) With Postpartum onset
    f) In addition – in partial remission, in full remission, or mood-congruent psychotic features, mood incongruent psychotic features, with full interepisode recovery, without full interepisode recovery, with seasonal pattern can be specified.

    Nowhere in the DSM can any specifyers be find for example about co-existing, co-morbid migraine, toothache, anger, or anxiety, regardless of how frequently or infrequently that occurs. In reflecting the modern terminology and current view, the DSM since DSM III-R specifically allows more than one Axis I (co-morbid) disorder to be listed and coded as diagnosis. These co-morbid conditions are targeted separately with treatment. Therefore no exclusions in the claims about with or without migraine, anxiety etc should be made. We have never claimed the treatment of anxiety with our method. The following should be more evident from the example under 2). This aproach is also supported by the PTO's viewpoint on other OAs [see 1)-B)].

However, we also would like to address the issue of treatment resistant depression (TRD) and non-TRD, and that it was appropriate to include that in the exclusion as it is relates to or is part of the psychosis specifyer. We have noted in our utility (page 3 line 21-24) that 'Nierenberg (1992) had noted that the cause of treatment-resistant depression may be an unrecognized psychosis, that may explain – at least in part – of why the "treatment-resistant" depression group improved with the addition of an antipsychotic medication'. We do not want to contest at this point of why Tollefson was granted a patent if their claims are evident from this and other prior art (O'Connor, M. 1998). We simply want to point out that in our description the TRD or non-TRD strongly correlates with (or is part of) the psychosis specifyer. (As a *reminder* please see enclosed pages from DSM, [pages 375-6, 411-28.]).

1) **–B)** As an additional support, that **the PTO in other cases also considered the same viewpoint** the following should be noted: For example in regards to (any of the USPTO, EU and WO) Tollefson reference(s) on TRD, Eli Lilly was not required to exclude anxiety from their patients claimed for TRD. It was known prior to their application that antipsychotics are useful for the treatment of anxiety. Since treatment resistant cases are more severe, that TRD group in clinical setting would also certainly include a whole range of moderate and severe anxiety. **The PTO judged that no exclusion was required in the Tollefson's claims for anxiety**, thus **sharing the view that it is considered a separate disorder** and the treatment for anxiety is targeted separately.

2) DSM clearly separates depressive disorders from anxiety disorders, even though the two can co-exist and called co-morbid disorders as we also described that in our provisional application. (and re-introduced it in our reply to the 1st OA).

   Faour has never said that his treatment (targeting anxiety) **would make depression better beyond the removal and treatment of the anxiety component**. Therefore Faour did not enable his method for the treatment of depression. [see 10a)]. In contrast, because Faour says that the co-morbid anxiety makes the depression worst, therefore the PTO argued that the treatment of anxiety is considered the treatment of depression. The applicant traverses that conclusion being convincing as also seen in the following analogy:

   a) if a patient has a chronic back pain, and as a coexisting condition somebody would hammer the patient's finger that would make the patient's condition worst. In fact that can put the patient into an acute cardiovascular shock. However, (the 'treatment' of) stopping the hammering of the finger would not treat the original back pain condition. The same was true for depression and anxiety: At the time of our invention these were (and still are) considered two separate diagnostic categories (that can co-exist). Therefore the treatment of anxiety by antipsychotic is specifically targeted for that condition and not for the underlying depression. Furthermore, as it would be further elaborated [under 7) below] the PTO cannot conclude that without explicit remarks and reasoning Faour would expose almost half of the patients who do not have anxiety to the side effects of antipsychotics when anxiety is easily measurable by psychological tests and clinical assessment in an accurate and reliable way. So anxiety disorders and depressive disorders were and still are considered two distinct diagnostic categories even if they can co-exist. Therefore there would be no need to "exclude" anxiety as that is a different diagnostic category, and that what is targeted in Faour's method. We never had the treatment of anxiety in our claims.

b) Even if the DSM would extend it's current diagnostic criteria (which is basically similar to the SIGECAPS acronym (sleep, interest, guilt, energy, concentration, psychomotor change, suicide, – and mood) and include anxiety within the criteria of diagnostic symptoms of depression; a treatment of a single depressive symptom (aside of mood, or aside of targeting the serotonin/neurotransmitter levels) were not considered as treatment of depression at the time of our invention. Decreased sleep is part of the depressive symptom list, but sleeping pills were not considered to be a treatment modality of depression, and none of the true sleeping pills were approved by the FDA as an antidepressant. So even if a separate treatment modality would target a depressive symptom or co-existing condition, they were not considered as the treatment of depression at the time of our invention.

It was only us who draw attention on how various substances have an antidepressant effect through an indirect mechanism of action (also called "pseudo-placebo effect" in one of our patent applications). We further showed of how these indirect medication effects plays a role on psychological effects (with high placebo percentage) and how these in turn have a change on the neuroplasticity [and gene expression].

It was only us who came up with a good number of reasoning of why the antipsychotic medications due to all these reasoning as a whole, should be used (as initial treatment) for the treatment of depression.

3) The above [1) and/or 2)] should suffice as an argument by itself. However, in addition, we have shown in the faxed Figures 1-3 that the clinician also has to take into consideration the practice guidelines and specifically address if there is a strong teaching against the method. The risk benefit alternative analysis is necessary for enablement for a new method. We have detailed the side effect problems and alternative methods, and we have also provided extensive list as secondary factors in our reply to the 1st office action. The Texas algorithm also includes the use of atypical antipsychotics but not as first choice, only if other alternatives fail. Faour's teaching is in concordance with that as we shall analyze that in reference to the less restrictive alternatives:

4) It is accepted in the psychiatric field that the least restrictive measures and the least restrictive setting have to be used first. This is also a patient right issue. It also makes common sense to try a method first that has the least side effect. The PTO also acknowledged that in the 2nd OA. Faour does not go through why that treatment should be used over other alternatives.

5) It is respectfully submitted that the PTO examiner errs with his line of reasoning (e.g. page 27 of 2nd OA).

First, the PTO is basing the obviousness rejection that Tollefson reported a method of "rapid onset antidepressant action", but despite of our specific question the PTO failed to come forward to show that where was the rapid onset action by Tollefson also demonstrated for non-psychotic, non-TRD patients.

Second, the PTO disregarded our proofs that the same authors published that the antidepressant monotherapy was effective in the same time frame as the combination treatment, therefore no "rapid action" can be contributed to the combination treatment reported by Tollefson in his TRD study.

Third it was also disregarded, that safer and even faster action antidepressant methods were previously published than the antidepressant-antipsychotic combination. **Therefore the tenets**

of the PTO reasoning are not-convincing as a line of argument motivating the artisan to use our method as initial treatment.

Fourth, - as far as the PTO's statement (e.g. page 27 of 2nd OA) of "One of ordinary skill in the art would reasonably have expected success in administering treatment as soon as possible to prevent suicide because suicide is known to correlate strongly with depression, and **because treating a subject for a serious condition as soon as possible is a generally recognized practice in the art**" the following should be noted: The applicant has presented a vast number of secondary factors (including the Texas algorithm) that in case of medication management of the depressed patients (even with suicide) showed that that line of the PTO's reasoning was not the accepted modality in the art. No combination of antipsychotics were administered as initial treatment. The standard practice was to admit the patient to a psychiatric ward and use medication "treatment as usual".

During the course of the applicant's curriculum in medical school the difference between the lay person's thinking and proper medical reasoning in emergency cases were specifically brought to attention. In a vehicle accident the lay person feels relieved if five patients are jammed into a small car to transport them to the hospital, but the proper care is to stabilize the patients first prior to transport. The lay person's thinking is different from the guidelines and the practice of "standard of care" that the clinicians must adhere to. Similar guidelines were present in psychiatry on the use of the least dangerous alternatives first and reserving the combination treatments for later for the failed treatments.

The accepted method for treating a suicidal patient at the time of our invention (and at present) is to observe and admit the patient to a psychiatric unit. In addition medication is started if the patient is not on any, (or the medications may be changed or adjusted if it was ineffective given sufficient time for response). ECT is another option but even that is rarely ever done on an emergency case in the middle of the night.

a) So in starting a medication in a patient with depression, an antidepressant is chosen. However, antidepressants like SSRIs are also efficacious for the treatment of anxiety disorders and comorbid/coexisting anxiety. Many (but not all) of the SSRIs had been also approved by the FDA for the treatment of various anxiety disorders, yet sometimes even the non-FDA approved SSRI's are used off label for the treatment of anxiety disorders. While some SSRIs got only FDA approval for some of the anxiety disorders, paroxetine got approval for all of these subgroups as well as for depression. So the least restrictive method is to treat the patient with an SSRI. There are sufficient number of publications on the effectiveness of the antidepressants for both anxiety and depression, and that a single antidepressant is effective for the treatment of co-occurring anxiety and depression. **(Goodnick PJ at al Mirtazapine in Major Depression With Comorbid Generalized Anxiety Disorder. J. Clin Psychiatry 1999, 60:7, 446-448, Silverstone PH et al Efficacy of Venlafaxine Exended Release in patients with Major Depressive Disorder and Comorbid Generalized Anxiety disorder. J. Clin Psychiatry 2001 (July), 62:523-529, Triverdi MH et al. Do Buproprione SR and Sertaline Differ in their Effects on Anxiety in Depressed Patients J. Clin Psychiatry 2001, 62:10, 776-78 (also presented in conferences in 2000 and 2001), Birmaher B et al Fluoxetine for childhood anxiety disorders. J. Am Acad. Child Adolesc. Psychiatry, 33:7 1994, 993-999).**

In addition it had been noted about the SSRIs in regards to the comorbid panic disorder that increases the risk of suicide the most, that "further benefit of this class of compounds, particularly in patients with comorbid panic and depression, is their ability to reduce suicidal ideas in comparison with other classes of antidepressant, and paroxetine has been shown to protect the patient against emerging suicidality". (page S21 second column paragraph under SSRI lines 5-10 of **Dunner DL. The issue of comorbidity in the treatment of panic. International Clinical Psychopharmacology 1998, Vol 13 (Suppl. 4) S19-24.**) The skilled in the art knows of when to use a particular SSRI (e.g. mirtazapine, or paroxetine over fluoxetine and vica versa), when also treating comorbid anxiety.

b) Buspiron (Buspar) is a known anti-anxiety agent and it was also used as adjunctive medication for TRD. It is generally safer than the antipsychotics which have the severe (TD & NMS) side effects. Appelberg had shown that after the first week of double bind treatment there was a greater reduction in depressive symptom compared to placebo. Please also note that the "rapid onset" of the antipsychotic as referenced by the PTO in the Tollefson article was also within the same time frame. So an argument of using the Faour's method with an antipsychotic would not be convincing in light of this reference, and in light of the risk/benefit alternative analysis that as we said the clinician must adhere to. **(Appelberg B.G. at al. Patients wih severe depression may benefit from buspirone augmentation of selective serotonin reuptake inhibitors: results from a placebo-controlled, randomized, double-bind, placebo wash-in study. J Clin Psychiatry. 2001 Jun; 62(6):448-52.)**

It should be also noted that the Appelberg study left in GAD (Generalized Anxiety Disorder) as comorbid condition within the group of depressed patients while excluding other conditions like psychotic depression and bipolar disorder. Buspirone was approved by the FDA for the treatment of GAD. Therefore Appelberg was treating comorbid anxiety with depression augmenting the antidepressant with buspirone. (Safer alternative).

c) In discussing yet another alternatives, anxiolytics can be added temporarily for the treatment of comorbid anxiety (and meanwhile the suicidal patient is still admitted and observed on the ward). It has been known to the art (as I was taught that as a resident which was prior to my patent application) that short acting benzodiazepines like lorazepam have a short half-life as it wears off and the blood level gets lower, and that can lead to (mini) withdrawal and the increase of anxiety before the next dose is administered. Lorazepam and the short acting benzodiazepines are used in acute settings but generally (preferably) should be avoided beyond the titration of the dose of benzodiazepams, because of the withdrawal effects before the next dose also reinforce the addictive nature of that drug. Long acting benzodiazepams like clonazepam (Klonopin) on the other hand have a steady state level without the withdrawal effect before the next dose. These are also considered mood stabilizers with added benefits, and are generally preferred over lorazepam. The short term use of long acting benzodiazepams do not possess the TD and the life threatening NMS, the side effects of the antipsychotics.

d) Anxiety is easily tested both clinically and through formal psychometrics. At the time of our invention and without specific guidance one could only target the treatment of anxiety if present. [see 2a) and 7)]. Faour's comment as referenced by the PTO is vague and not clear and therefore did not enable the clinician of the use of his method – as for the purpose of our claims. It would be logical for a clinician to specifically target the

anxiety when present, and also to use the safest alternative that we described under 5 a) and 5 b).

e) In light of Khan that showed that there were no significant differences in the rates of suicidal behavior between those treated with active anti-anxiety medications and those taking placebo, the reasoning to use Faour method for the "prevention" of suicide would be also questioned to be a solid and convincing line of reasoning. We on the other hand listed many additional reasons and explanation for the mechanism of action of the (added) antipsychotics (specifically through all of these combined actions) therefore enabling our method. **(Khan A et al Suicide risk in patients with anxiety disorders: a meta-analysis of the FDA database. J Affect Disord, 2002 Apr; 68(2-3):183-90)**

We have mentioned with sufficient emphasis that there is a strong teaching against using antipsychotics because of the side effects that includes the NMS and TD as well as newer side effects like diabetes and in some the weight gain. Some state law also requires written consent in inpatient setting for the use of antipsychotics. Nothing in the Faour reference was addressing of how to overcome the teaching against issue when safer alternatives are available. Any psychiatrist should know the risk of being sued over using these drugs even when precautions are used. That was definitely the issue with TD and NMS, but newly also with diabetes as the zyprexa-diabetes-lawsuit.com and similar pages with Google search of "olanzapine side effect and attorney" reveals. So the Faour reference is not enabling for that reason, but also on the following basis:

6) Faour have not specifically stated initial treatment, therefore in light of he specifically not addressing the strong teaching against the use of antipsychotics in non-TRD and non-psychotic depression, the skilled in the art would have used safer alternatives first (aside of a psychic or somatic anxiety of delusional or psychotic degree). Our invention therefore is distinguishable from Faour's, and contains new limitation. That new limitation is not obvious and the tenets of the PTO line of reasoning is not convincing [e.g. 5)].

7) As briefly mentioned under 2a) and 5d) (when we discussed that anxiety disorders and depressive disorders were and still are considered two distinct diagnostic categories even if they can co-exist) the PTO cannot conclude that without explicit remarks and reasoning Faour would expose almost half of the patients to the side effects of antipsychotics when anxiety is easily measurable by psychological tests and clinical assessment in an accurate and reliable way. Therefore the skilled in the art could again not been able to follow Faour's method as it was not clear and it was not presented in an unambiguous way.

We on the other hand listed a good number of reasoning that together enabled the use of antipsychotics as initial treatment of depression.

Even if all the above arguments would be ignored by the PTO (that I would be surprised of), we have introduced new limitations (in addition of the initial treatment) of giving the medication combination to:

a) substantially all of said patients (for the benefit of the group, that included much more reasoning than the presence of anxiety in 56% of depression), and (as in our provisional):
b) giving the antipsychotic antidepressant combination as a first choice of treatment that is changing the standard of care,

and therefore we are definitely addressing a different species than the co-existing anxiety. To arrive to the clinical decision making allowing or necessitating the use of our method a series of new steps need to be performed. The terms choice of treatment (or first choice of treatment) as well as the benefit for the group or the standard of care are well understood by

the skilled in the art. These terms do introduce new limitations and are drastically changing the patient population.

8) It is also respectfully submitted, that Faour did not discuss the low dose concept as we have demonstrated in our reply to the 1st OA. [and also see 10-d) below]

9) The PTO also stated during the interview, that it had been well established that not following the prior art does not mean allowance of patentability. We respectfully submit that the "prior art" was not followed as it was not enabled, and because our method is distinguishable from the prior art. We have mentioned that in our reply to the 1st OA that despite the intense media attention, and the long felt unsolved need, and other secondary factors our method was not followed and a strong teaching against continued. The surprising new solution of our method that we successfully enabled and that would fill that said long felt need cannot be said to be obvious in the light of all of the secondary factors.

10) It is submitted that the Faour reference is vague and is not presented in a clear and unambiguous way as regards to the subject of our invention. The Faour reference is therefore insufficient for enablement in regards of our claims:

a) Faour have not mentioned that his treatment (targeting anxiety) would make depression better beyond the removal and treatment of the anxiety component. Therefore Faour did not enable his method for the treatment of depression. (We on the other hand – for the first time in history - went through a detailed analysis enabling of how the treatment of one symptom through psychological effects and through neuroplasticity, would have an effect on the depression as a whole, and on the mood itself in an indirect way).

b) Faour did not specify of what type of anxiety was he intending to treat co-existing with depression. Anxiety is a heterogenous disorder, including generalized anxiety disorder (GAD), panic disorder with or without agoraphobia, obsessive compulsive disorder (OCD), post-traumatic stress disorder (PTSD), substance induced anxiety disorder for example. It is notable that Faour – according to the PTO – is not just hinting or raising suspicion as part of a series of argument to shift the balance toward considering the use of antipsychotics in combination with antidepressants in the treatment of depression, but the single – and in our opinion vague - statement by Faour – according to the PTO – would be sufficient as a clear guidance and be enabling. We traverse that reasoning being convincing.

c) Faour also did not mention of the degree of anxiety needing to be present – mild moderate or severe – in order to justify the use of his "method". Faour did not specifically stated to use his method right away as initial treatment. In fact it would have been surprising of skipping safer effective other available alternatives and do that without sufficient reasoning as for why to skip them. [see 5) above]. [As a side note in our provisional application 0186 lines 5-6 we have described that Kaplan have used an atypical antidepressant with a newer antidepressant for TRD cases with "near-paranoid" anxiety.] The artisan/clinician may feel justified to give antipsychotic in the psychotic spectrum, but would need a strong argument and specific enablement for skipping less dangerous alternatives for mild to moderate anxiety not in the psychotic spectrum. Such disclosure or enablement for risk/benefit/alternative analysis was not provided in the Faour reference.

d) Four has not excluded any atypical antipsychotic for his method. There was also no low dose concept in the Faour publication and for olanzapine Faour's dose range included 0.25-50 mg far exceeding the FDA maximum dose (e.g. in claim 7). It had been known that olanzapine has treatment induced side effect that includes anxiety, agitation and

akathisia. **(Beasely CM et al Olanzapine versus placebo and Haloperidol. Acute phase results of the North American double-blind olanzapine trial. Neuropsychopharmacology 14: 111-123 1996)**. In fact that paper specifically suggested some potential pharmacological contribution for more agitation, nervousness and anxiety with higher doses of olanzapine than with placebo. (page 121 second column lines 7-10.) The treatment emergent akathisia occurred with olanzapine high doses approximately one-half rate with haloperidol. (page 121 second column lines 46-47.) Now it was also well know in the art with sufficient media publicity surrounding the law suit well over a decade prior to our application, claiming that fluoxetine was causing suicide, and that akathisia (restlessness) caused by the antidepressant may be the causative factor of these suicides (even if - as for the group - the suicide rate was decreased on the SSRI antidepressant which was much safer than the TCA in case of overdose).

So Faour would not enable the artisan to follow the interpretation of PTO - as being enabling for the purpose of our claims - as he was not discussing the low dose in his specification, and not going through the risk benefit analysis of the extrapyramidal side effect of the antipsychotics. Faour is also vague and not unambiguous in general with his description (that in part was further interpreted in certain specific ways by the PTO). How would the balance be shifted toward using Faour's method in targeting the treatment of anxiety with the use of antipsychotics, if the very same antipsychotics at high doses also elicit anxiety that they are supposed to reduce; and if the very same antipsychotic at high doses may also elicit akathisia – linked to treatment emergent suicidality, and when other alternatives with less serious side effects were available for the treatment of anxiety, and if Faour's description is otherwise also vague (e.g. which type of anxiety is targeted and at what severity)? We on the other hand went into a detailed guidance in regards to the extrapyramidal side effects, akathisia (e.g. page 4 line 19 of the utility) and other factors, and listed many other reasons that together would allow and necessitate the use of the antipsychotics (at a low dose) for the purpose of our claims. We also had new limitations like the initial treatment. It is respectfully submitted that clearly the Faour reference lacks enablement.

e) Faour also did not give guidance about the risk/benefit/ alternative analysis that we mention separately under 3)-5) above.

f) Faour's description would be confusing as interpreted by the PTO as there is no mentioning if Faour would or would not want to expose about half of the patients who do not have co-morbid anxiety. [see 7) above.] It would be not clear for the average artisan of on what basis can that argument be defended, but most likely the average artisan would not even think of that interpretation since nothing was said about that possibility.

g) No synergism is mentioned in Four's reference on antipsychotics and antidepressants potentiating each other. No enablement was given by Faour in this regard either. We on the other hand enabled this with the reasons of how the antipsychotics act, and on how a single change of even the "extended" depressive symptoms through psychological and neuroplasticity [and gene-expression] changes would affect a better and more effective treatment of the depression.

h) There is no mentioning or enablement in the Faour's reference on that method being effective

   A) for the treatment of cognitive distortion, (and thus through a different mechanism being effective for the treatment of depression as well)

B) for the treatment of paradoxical effect of antidepressants worsening depression or causing suicide or suicidal ideation,
C) for the treatment of tolerance developing with antidepressant treatment,
D) for the treatment of resisting recurrence of depression ("prevention of relapse")
E) for treating the residual symptoms of depression
F) for treating substantially all patients for the benefit of the group,
G) for the treatment of first choice (as that term is understood in the art)
H) wherein the antipsychotic is given in a low dose approximately in the target range of $1/3^{rd}$ of the dose usually given for psychosis
I) for a method of smoking cessation or nicotine withdrawal,

i) It becomes evident that our method is distinguishable from Faour, and that Faour reference is vague as regard to our invention and Faour has not presented a clear and unambiguous guidance and not enabled his method in regards to our claims.

Therefore we respectfully request of the withdrawal of Faour as prior art.

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ... **Anticipation only occurs if the prior art reference [is] <u>teaching each and every element of our claims</u>.**
If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention**."

If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn. (In re Rouffet, 149 F.3d 1350 [Fed. Cir. 1998].) (Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223.)

The anticipation did not occur as it was the PTO and not Tollefson that came up with the "explanation that was based on non-convincing reasoning/false logic" leading the clinician to commit malpractice by skipping required steps. For these exact same reasons of skipping steps Tollefson did not teach each and every element of our claims! (The unconvincing line of reasoning originating from the Tollefson reference was carried over directly or as an implication to the Faour reference as well.) Since the PTO's erroneous presupposition "unconvincing line of reasoning" would lead the artisan to commit malpractice the PTO did not present a convincing line of reasoning for obviousness and therefore the rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

The artisan would also need solid reasons for overcoming the strong teaching away and discouraging of using the combination therapy for the purpose of our claims (and such disclosures were not given by any of the cited prior art or the PTO). "A reference teaches away when a person of ordinary skill, upon reading the reference, would be lead in a direction divergent from the path that was taken by the applicant. (In re Gurley, 27 F.3d 551 [Fed. Cir. 1994].)

In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

Further notes on the phone interview (post 2nd OA).

- It is respectfully submitted that we did not discuss all claims or all aspects / possibilities for allowance for all claims, specifically e.g. for

a) Cognitive distortion,
b) resisting depression and suicide,
c) inhibiting the paradoxical effect of the antidepressant to cause suicide,
d) our method for treating partial depression,
e) smoking cessation.

- The **tenets of all lines of reasoning of PTO on obviousness** by Tollefson, Chappell and Faour laid on the "rapid onset" disclosed by Tollefson in TRD (wherein even the said "rapid onset" was not substantiated compaired to monotherapy published by the same authors) and as further interpreted by the PTO. – No answer was received where does it say in the cited Tollefson reference that the rapid onset was demonstrated in clinical studies for non-TRD. The PTO could not withdraw its statement in this regard as "junior examiner was not allowed to, but he said that he can see that "Tolefson meant it only for TRD". We further elaborated on this topic in our reply elsewhere.

- Faxed copies of Figures 1-3 were presented to the PTO at the phone interview.

- Main points from the "**Theory**" (from reply to 1st OA) were verbally presented to at the interview. PTO examiner listened to the applicant, and did not find our theory or reasoning irrelevant or non-existing at this time.

- After that the PTO came up with new lines of reasoning on Faour – the answer was discussed above separately.

- **New matter** on "substantially all <u>of said</u> patients" was basically withdrawn after the clarification, even if it was not phrased exactly this way. (I assume that in the letter the PTO meant "**intended use limitations**" for this.)

- **New matter** on <u>metabolite of risperidone</u> was presented as basically it appears in this written reply. The PTO has maintained its opinion based on that the pharmacokinetics might be different –without saying it how. The applicant has mentioned that if the other claims [with the amendments] would be allowed, it probably would not be worthwhile to contest this part further.

- **Secondary considerations with respect to prior art** were brought up, and the PTO's response and our response is discussed in this reply later.

- **Enablement for broad classes of therapeutic agents** was discussed. The PTO examiner said that "I'm not familiar with the EU rules for allowing Tollefson broad classes of drugs". He mentioned US applications as well. Our reasoning appears later in this written reply. Never the less claims 1-3 were amended.

- **The Definition of low dose** was discussed. No final agreement was reached. The PTO's suggestion (of giving a specific range in the claims) may not be workable. To the question of deleting low dose (that the applicant strongly considers if this remains a barrier), the PTO said every difference from prior art would serve the applicant's benefit. There are more detailed arguments at various parts of this written reply on the low dose as it was defined in our specification, and as it is in contrast to the prior art.

- The PTO stated it is possible to add **amendments to the specification from provisional**, (with attention to exact pasting, and that grammatical correction is allowed (we clearly marked that).

The applicant **request for help from the PTO** was also brought up at the phone interview. The PTO's reply incorporated basically three areas.
1) The PTO encouraged the applicant to find an attorney. (In this written reply specifics are given on the difficulty this applicant has encountered in finding a qualified registered patent attorney with background/ undergraduate degree in this field, who do not have conflict of interest with "big pharma". Furthermore, it is pointed out that in this field – since usually expensive studies are required for enablement – no competent patent attorney with specialty in that field would survive serving only small entity inventors and not having the conflict of interest with "big pahrma".)
2) The PTO examiner did offer some suggestions – some workable some were likely not (even as acknowledged by the PTO at the phone interview that his suggestion may be considered new matter [and thus would be rejected]).
3) The PTO stated that they cannot prosecute my application. If that is meant that they cannot help applicant with crafting the claims, and suggesting how to come around the objection, than it is in high contrast of this applicant's knowledge on the PTO's regulation, (and by his reading patent books) that specifically suggest that indeed the PTO in pro se (no attorney) cases should actively help the applicant in these specific areas and the claim(s). See also #14 at page 34, and enclosure listed above as "**1c) A14** (highlighted in the enclosure) **A request for claim-drafting assistance under MPEP 707.07(j) ... (Showing that the PTO has to give assistance in claim drafting** – which is against the PTO statement in the interview. **From Patent attorney David Pressman, Book: "Patent it yourself". Nolo, 2004 10th edition, page 13/46."**

Continuation of the Reply to the 2nd OA

(including reference to the interview that was done after the 2nd OA):
(This part was prepared before the phone interview. However it was changed to incorporate any parts from the phone interview that was not yet fully addressed.

In order to continue to reply to the 2nd OA it is best to get certain confusions and PTO errors and unconvincing line of reasoning out of the way specifically those that were often repeated in the OA(s).

So addressing these separately from - 2nd reply **#1);** - 2nd reply **#21);** would be more efficient rather than repeating them often in the line-by-line reply.)

> **It needs to be positively acknoledged, that:**
> The 2nd OA acknowledged enablement for cognitive distortion but not on any antidepressant and any antipsychotics. (page 5 of 2nd OA last 3 lines, and page 10 lines1-6). PTO acknowledged the art being crowded as regards to classes of drugs currently known to be psychiatric drugs. (page 12 of 2nd OA lines 2-5.)
> Yet no claims were allowed despite of the facts that a number of claims have listed only currently used medication combinations.
>
> PTO further acknowledges (page 19 of 2nd OA lines 16-18.), that the specification is enabling for a method treating depression and associated conditions, and avoiding, protecting against, or remedying relapse or recurrence of depression (but not for preventing depression or suicide).

We will highlight some of the PTO errors here under numbered heading (e.g.#1) followed by our "line-by line reply to the 2nd office action **at page 46** with more details at times:

These numbered headings/ points would be essential in pointing out of why our invention and claims are distinguishable form prior art, and that at what points were the PTO's line of reasoning unconvincing, and for what reasons.

- 2nd reply **#1);** The PTO is acknowledging in page 16 of the 2nd office action that "The usual practice in the art is to diagnose a patient ... before deciding on a course of therapy, and to administer therapy only to patients reasonably believed to benefit from said therapy. The benefits of this approach include the avoidance of unnecessary side effects and the improved efficacy of therapy..."
The PTO also (at page 16) acknowledged that "antipsychotic drugs possess such severe and potentially life-threatening side effects." The PTO continues "antipsychotic drugs are only known to be of benefit from patients having a psychiatric disorder involving psychosis or psychotic-like symptoms. ... Subjects not having these conditions will experience the side effects of the drugs without any benefit. Thus these drugs must not be prescribed without careful consideration of a patient's situation and whether the patient will benefit from them."

Therefore the PTO has acknowledged (at other place, at page 16) that the Tollefson reference in the risk over benefit analysis is harmful (for the purposes of our claims) (see Figure 1.) [as Tolefson did not enabled the clinicians for any such benefits for the purposes of our claims]! This "harmfulness" of the Tollefson technique is what in the 2nd office action the PTO demands from us and erroneously states (at page 28 of the final action): "Applicant does not demonstrate that the method of Tollefson (and thus Applicant's own method) is in fact harmful". **This PTO statement is the opposite to the facts.** We have specifically stated in our reply 22 (page 60 lines 15-19, 24-27, 32-34 & page 62 lines 7-14,) that without disclosing the benefits over the risks the artisan could have not used Tollefson's technique for our invention, and would have committed malpractice! The PTO has disregarded this and the referenced law that **"the examiner cannot use references as prior art if such references have insufficient disclosures." In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public..." (page 60 lines 35-42).** The PTO also disregarded the strong supporting secondary factors (pages 93-99) and additional paragraphs of the referenced law (page 98 lines 15-40). Namely, and in putting all of our arguments together (see also page 98 lines 23-31) **the examiner did not "present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of**

the references" if the PTO assumes in the PTO's reasoning that the artisan would skip clinical steps and be willing to commit malpractice in order to follow the PTO's unconvincing line of reasoning. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

> There are important factors to consider as regards to the prior art like the differences in the function of the invention (In re Ellis, 476 F.2d 1370, [C.C.P.A. 1978].) (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223). Our claims are aiming a diferent patient population and a new use.
>
> The skilled in the art would be discouraged in following the path (that the PTO recommends) or would lead in a direction divergent from the path that was taken by this applicant. (In re Gurley, 27 F.3.d 551 [Fed. Cir. 1994].) (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 224).

The above PTO's statement ("Applicant does not demonstrate that the method of Tollefson (and thus Applicant's own method) is in fact harmful") is false twice (or more) within one sentence: Just because the Tollefsen's method would be harmful for the purposes of our claims **without** disclosure, if not showing any benefit but only risks over known treatments – (and this is the logic that PTO acknowledged on page 16), that does not mean that **with additional inventive steps** and with adequate **new disclosure** the applicant could not prove that contrary to the prior art and the customary standard of care, (secondary factors) the combination method would not only be not harmful **for the new use**, but a preferred and a "must use" method. Therefore just because Tollefson's reference was harmful with the lack of disclosure (and lack of enablement) for the purposes of our claims (that is without the adequate risk benefit/alternative analysis), a new disclosure for the new use **and** with the provided further steps can still make the combination method the subject of an invention. (See also Figure 1, 2, and 3,). In addition we had new limitation (non-TRD, and for initial treatment and for cognitive distortion etc). So with the above statement the PTO has made erroneous conclusions with a non-convincing line of reasoning! The PTO has cited the Wands factors *and Genetech,* 108 F.3d at 1366, that sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (We emphasize here the underlined parts!)

This is what we were also stating in our reply in explaining the risk benefit analysis. Please see Figure 1. [Where A is an antidepressant and B is an atypical antipsychotic, then
using risk/benefit/alternative analysis → if A is as rapid as A+B and B has even life threatening side effect then there is no benefit to use A+B over A. Therefore by doing this analysis the clinician is not permitted to use the combination (unless other info or guidance was disclosed by Tollefson, (but it was not the case).] (See also Reply-22 and Reply-26 to the 1st office action at pages 59, 73,)

Furthermore, the PTO is also asking that the applicant would need to show that "for the Tollefson reference there exists no case in which their method would be preferable to no treatment at all". (page 28)

The PTO is using an erroneous logic again as if the PTO's own conclusion – with it's tenets never being substantiated – would have been said by the prior art reference and this was not the case. Therefore the PTO pretends that their line of (not convincing) argument was included in the prior art when it was not.

The PTO disregards the important information that Tollefson never ever said that their combination therapy because it is for (never substantiated) rapid action can be and should be therefore used for a treatment of depression given right away as it would be logical for a fast action treatment. This was only the PTO's speculation (with the PTO's tenets of Tollefson demonstrating rapid action in non-TRD **not being ever substantiated**) in rejecting our claims. The PTO further disregarded our argument and skipped important steps in coming to their (the PTO's) conclusions that a clinician could not follow without doing malpractice. Therefore the PTO's logic is false and unconvincing! This would be further explained below and in Figure 1 **(at page 21)**.

- 2nd reply **#2);** The second office action in this matter maintains their own prior (erroneous) presupposition that because Tollefson stated that the combination therapy (for TRD !) is a rapid action (within a week) therefore it should be used as initial therapy especially for emergency cases in preventing suicide. The facts that a clinician should also do a risk benefit analysis was left out. Our written argument on that was ignored by the PTO. If **a single medication by the same author** Tollefson **was shown to be effective within the same time frame** within a week, **than the combination therapy does not have any benefit over monotherapy**. We did point this out in our reply (that again was ignored by the PTO). Therefore the PTO's conclusion of "logical" to use a combination treatment with added and even life threatening risks over the monotherapy of the single agent that is even faster acting is matter of fact incorrect and not convincing. The PTO's logic is not supported by facts but the other way around, the facts talk against the PTO's logic. No reply was given by the PTO to this argument. The PTO's statement and demand for the applicant needing to show that for Tollefson reference there exists no case in which their method would be preferable to no treatment at all is not what decides on this issue, but mere demonstration that the PTO's logic is false (and not-convincing), and **that the aforementioned (erroneous) conclusion was not in the prior art!** Therefore the PTO (repeatedly) did not have a convincing line of reasoning and the prior art objection should be withdrawn.

The PTO's unfamiliarity with the customary and standard of care is further discussed in Reply Q (q) at page 64.

In addition we have also shown in our first reply that prior art had even faster acting and safer monotherapy than Tollefson's combination treatment and Tollefson failed to go into any risk benefit alternative analysis in regard of why the combination treatment would be better than monotherapy, and therefore for the average clinician that cited prior art was not disclosing as regards to our claims. As we stated in our reply to the first office action:

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ... **Anticipation only occurs if the prior art reference [is] teaching each and every element of our claims.**
If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention.**"

If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn. (In re Rouffet, 149 F.3d 1350 [Fed. Cir. 1998].) (Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 223.)

The anticipation did not occur as it was the PTO and not Tollefson that came up with the "*explanation* that was based on unconvincing line of reasoning" leading the clinician to commit malpractice by skipping required steps. For these exact same reasons of skipping steps Tollefson did not teach each and every element of our claims! Since the PTO's presupposition and "false logic" would lead the artisan to commit malpractice the PTO did not present a convincing line of reasoning for obviousness and therefore the rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

The artisan would also need solid reasons for overcoming the strong teaching away and discouraging of using the combination therapy for the purpose of our claims (and such disclosures were not given by any of the cited prior art or the PTO). "A reference teaches away when a person of ordinary skill, upon reading the reference, would be lead in a direction divergent from the path that was taken by the applicant. (In re Gurley, 27 F.3d 551 [Fed. Cir. 1994].)

In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A patent or printed publication is an insufficient disclosure if it is not enabling." "The examiner cannot use references as prior art if such references have insufficient disclosures."

"A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public, meaning that someone with general skill in [the] field could have used the reference's description of [the] invention with their own knowledge to make [our] claimed invention themselves." (In re Wilder, 429 F.2d 447 (C.C.P.A. 1970).)

As stated above Tollefson in skipping important steps and not going into the analysis that is only the PTO's explanation now (and is leading to malpractice), the Tollefson reference is an insufficient disclosure as it is not enabling, and did not put the subject matter of our claims in the possession of the public.

The PTO also disregarded our cited argument and the cited law!

This was explained in our 1st reply but is further explained in Figure 1 below:

Figure 1.: Examples of how the PTO examiner lines of reasoning is not convincing as it skips steps that would lead a third party (clinician) to consequent faulty logic. The PTO is not thinking as the skilled in the art has to. (The PTO is leaving out the risk/benefit/alternative analysis that would lead the clinician to commit malpractice. We have stated that in our reply! Yet the PTO skips that and repeats that his "logic" would be logical to the clinician, and that the clinician (without our guidance and enablement) would had no problem of following the PTO's line of reasoning (and skipping steps) and come to the same conclusions as the teaching of our invention and claims: (In doing so the non-clinicians would be charged or imprisoned for practicing medicine/psychiatry without license, and the clinicians would loose malpractice cases of not doing the risk/benefit/alternative analysis, and being negligent!)

- Example of the non-convincing line of reasoning (illogical faulty thinking) by the PTO examiner:
Rapid onset of combination drugs: if A is as rapid as A+B, and A+B has no proven or explained benefit over A alone but B has potential lethal side effect; and in addition there is C that is an antidepressant monotherapy that is even faster acting then A, or A+B then the

PTO states (that would lead any clinician to commit malpractice) that:

A+B ----------(PTO skipping steps)----------→ use it (A+B)

(that is the PTO states that the average clinician would chose to commit malpractice and skip the required steps, and use this as initial Rx, and for non-TRD and non-psychotic depression without guidance and reasons, that is without enablement)

(PTO further errs on several other things, that is Tollefson never made the conclusion that the PTO stated would be logical to the skilled in the art, but in fact it is only the reasoning of the PTO, and only if the PTO disregards our teaching - that they did.)

- Instead the **clinician** is obligated to think differently:
(using drug A+B)

Step one:

A+B → use risk/benefit/alternative analysis →
(if A is as rapid as A+B and B has even life threatening side effect then there is no benefit to use A+B over A. Therefore by doing this analysis the clinician is not permitted to use the combination (unless other info or guidance was disclosed by Tollefson, (but it was not the case).

End result → for the skilled in the art
do not use it (A+B); it leads to malpractice!
(Do not use A+B for initial Rx for non-TRD non-psychotic depression)

Step two:

If there is C that is an antidepressant monotherapy that is even faster acting then A, or A+B and C does not have B compound's potentially lethal side effect and is generally accepted as safer than A+B then

End result → for the skilled in the art
do not use it (A+B); it leads to malpractice!
(Do not use A+B for initial Rx for non-TRD non-psychotic depression)

Step three; another step: the clinician should also compare his decision to the current standard of care (including teachings against our inventions that we have included in our 1st reply).

End result → for the skilled in the art
do not use it (A+B); it leads to malpractice!
(Do not use A+B for initial Rx for non-TRD non-psychotic depression)

Presented secondary factors also supported this, but again the PTO examiners disregarded that too in order to maintain their unconvincing line of reasoning. With that the PTO denies our claims and builds up to other erroneous conclusions.
On the other hand we have provided enablement to overcome these barriers, and this was presented in our application and claims.

- 2nd reply **#3);** (Please also refer to the earlier part of this reply, the reply to the phone interview in regards to Faour. This part replies to the 2nd OA and was prepared prior to the phone interview. The information in this part still stands as for the reply to the written 2nd OA.)

In a different matter the PTO states in the 2nd office action (page 32) that because a wider patient population was mentioned therefore Faour disclosed the patient population in our invention and the person with ordinary skill of the art would have had no difficulty practicing our invention. The PTO was disregarding our arguments of why clinically the cited prior art was non-disclosing and not enabling in regard of our claims. In fact the PTO falsely stated that I provided no evidence that Faour was not enabling. (See Reply 23 page 67 of our reply to the 1st office action – in the context of our other arguments). (Further evidence that the Faour reference is not enabling – including the new line of reasoning brought up at the phone interview – was provided here from pages 6-15.)

Further inventive steps are needed to use our method for the disclosed subpopulation of the broad depressive diagnostic category. (Bipolar disorder and MDD with TRD has high prevalence where psychosis goes unnoticed – as disclosed and referenced by prior art – and is different for unipolar non-psychotic, non-TRD subpopulation). **Generalization for all depression (broader term) needs enablement.**

The PTO was again disregarding the fact that the clinicians need to go through a risk benefit alternative analysis before they can apply a treatment modality in order to avoid malpractice. Faour did not provided any explanation, guidance, or enablement – in a clear and unambiguous way - of why their method would be useful and showing any benefit for non-psychotic, non-treatment resistant depression as initial therapy (or for the purpose of using our claims). Faour also did not have a risk/benefit/alternative analysis, or the new limitation of initial treatment. A mere mentioning of a broad or very broad diagnostic category (like depression or all of the mental illnesses in the DSM) would not be sufficient explanation for the one skilled in the art to deviate from the standard of care. Even for off label use of a method the clinician needs to have a good and solid reason (or better yet reasons) to go against the standard practice and the strong teaching against the method for that subpopulation of a broad diagnostic category. Going against the standard of care is a malpractice (unless solid reasons for the benefit of the patient are explicitly spelled out and are documented in the patient's chart). This is known in the medical risk management field that we have specifically referenced in our 1st reply page 60 lines 16-20, & page 98 lines 28-31. Therefore the ordinary clinician could not have used Faour's method over what was already known at the time of our invention, that is could not have used Faour's method for the purpose of our claims. This was very specifically spelled out in our reply (Reply 23) to the first office action but that too was disregarded by the PTO.

The PTO again did not have a convincing line of reasoning and the prior art objection should be withdrawn.

> We also would like to give an analogy to show that extrapolating to our invention the PTO's line of reasoning is not convincing as regards to Faour's patent on their delivery method. Our clinical reasoning in this matter is more precise than the following general analogy, never the less it is worth mentioning:
> With the logic the PTO was using the PTO is saying that in the age of Leonardo Da Vinci if there would have been a patent on delivering wheels to carpenters for building vehicles that would have prevented to put a wheel on an aircraft (on a subcategory of a vehicle), even when wagons were the

only vehicles existing at that time. (Let's disregard the fact that there were no patent laws at that time. The example still underlines the error in the PTO examiners' thinking.) The error lies in that, there are additional steps required to be overcome the obstacles for the aircraft, (like for the wheels to withstand the impact of landing) and that was not described and enabled in the prior art.

Another example: If there would be a prior art stating that vehicles with wheal are stable, the artisan (costumer) would not want to buy a car with one wheal! Additional steps are required to make use of such invention (like the wheal chair with gyro and computer stabilization that can clime on stairs). General statement on a big category does not necessarily true for a subcategory. Overcoming the obstacles with additional steps would make the invention patentable or would make it even a new use!

The arguments in our clinical example and claims are even stronger then this analogy, as we have shown, that our invention was not enabled in the prior art, and that is why the PTO's line of reasoning was not convincing.

Although our previous clinical line of argument regarding the treatment of depression was explained in our 1st reply, let us further explain it in Figure 2 below (and continue with other arguments under #4):

Figure 2.: Examples of how the PTO skips steps with unconvincing line of reasoning and is not thinking as the skilled in the art has to. **PTO states (that would lead any clinician to commit malpractice) that**: Faour (in describing a delivery method), Chappell, Tollefson, or as we add to this list now, Nesbitt and Pharmacia & Upjohn company's WO 02/053140 A2; or Tollefson's EP 0966967 A2; Tollefson's EP 0958824 A2; or Ralph and Pfizer's EP 1238676 A1 (or any other prior art that was brought to our attention up to date), or **the artisan would have followed the PTO's reasoning**:

A+B is used:

- for the wide definition of depression *(therefore the PTO states the non-TRD and non-psychotic depression should be understood in that term **against** the current practice of the standard of care, and despite the fact that the cited prior art was not disclosing of why and for what benefit A+B should be used at all or specifically as initial treatment for these subcategories i.e. the non-TRD and non-psychotic depression, (therefore the PTO is skipping clinical decision making steps)*, or
- for more broader mental illnesses (including depression – "– [ditto all italics from above]), or
- for an even broader term, that is for all of DSM diagnosis, for all of mental illnesses (that the WO 02/053140 A2 have explicitly incorporated as reference) (-"-[ditto all italics from above])

"therefore – as per the PTO - the skilled artisan would had no problem in applying the method for non-TRD and non-psychotic depression as initial Rx"

PTO's end result ----------(PTO skipping steps)----------→ use it

(that is the PTO states that the average clinician would chose to commit malpractice and skip the required steps, **and** use this as initial Rx, and for non-TRD and non-psychotic depression without guidance and reasons, that is without adequate enablement)

- Instead the **clinician** is obligated to think differently (using drug A+B):

Step one:

A+B → where is the disclosure that why that should be used also for non-TRD and non-psychotic depression?

There is none! -------- **End result**----------→ for the skilled in the art do not use it; it leads to malpractice!

Step two:

A+B → what benefit does A+B provide over known risks that warns against using it? Was there an adequate disclosure and enablement?

There is none! -------- **End result**----------→ for the skilled in the art do not use it; it leads to malpractice!

Step three:

A+B → why should that be used as an initial Rx? Was there an adequate disclosure and enablement?

There is none! -------- **End result**----------→ for the skilled in the art do not use it; it leads to malpractice!

Step four:

A+B → what benefit does A+B provide over known risks that warns against using it as an initial Rx? Was there an adequate disclosure and enablement?

There is none! -------- **End result**----------→ for the skilled in the art do not use it; it leads to malpractice!

Step five:

A+B → compare the use of A+B for non-TRD and non-psychotic depression as an initial Rx to the current standard of care and recommendations including teaching against its use and use the risk/benefit alternative analysis (and see if there was an adequate disclosure and enablement in the cited prior art in this regard).

There is none! -------- **End result**----------→ for the skilled in the art do not use it; it leads to malpractice!

Therefore by doing this analysis the clinician is not permitted to use combination for non-TRD and non-psychotic depression as an initial Rx (unless guidance was disclosed with adequate enablement by the cited prior art. (but that was not the case for any of the cited prior arts!)

Presented secondary factors also supported this, but again the PTO examiners disregarded that too in order to maintain their unconvincing line of reasoning. With that the PTO denies our claims and builds up to other erroneous conclusions. On the other hand we have provided enablement to overcome these barriers, and this was presented in our application and claims.

- 2nd reply **#4);** The same unconvincing line of reasoning (false logic) by the PTO is repeated with Chappell reference, disregarding our arguments again. (page 35) The same graph, Figure 2 above applies here too. The PTO again did not have a convincing line of reasoning and the prior art objection should be withdrawn.

The PTO does not follow a logic that is mandated for the clinical decision making therefore it is not based on facts. Moreover the PTO disregards our supporting arguments and the secondary factors.

The PTO cannot assume that the artisan would commit malpractice in skipping mandated steps in order to please the PTO and follow the false presupposition of the PTO.

Let us verbally describe the above graph (Figure 2) and further exemplify the error of what the PTO's logic would lead to:
The PTO assumes that the average clinician (the skilled in the art) would have had no problem of using the aforementioned medication combination as initial treatment for non-treatment resistant depression (non-TRD) and non-psychotic depression because Faour and Chappel were mentioning of a larger group; depression or mental illness.

This same PTO logic in the **WO 02/053140 A2 (page 14 lines 30-33, and page 15 lines 1-2)** application would be even more bizarre as in that reference an even broader term then depression is used: **WO 02/053140 A2 (page 14 lines 30-33, and page 15 lines 1-2)** application made an explicit reference to all of the mental disorders that the DSM covers and that their combination of treatment is good for all of these hundreds of illnesses covered in the DSM coding book. However that **WO 02/053140 A2 (page 14 lines 30-33, and page 15 lines 1-2)** reference is also without any guidance whatsoever of why to use the medication combination, in non-customary modalities (like non-TRD non-psychotic depression for initial Rx); and without any guidance whatsoever of what benefit would that modality give over other alternatives. In fact there is not even a mentioning of non-TRD non-psychotic depression for initial Rx in any of these references. Therefore that **WO 02/053140 A2 (page 14 lines 30-33, and page 15 lines 1-2)** application is also **without giving any enablement**.

> We need to point out the unconvincing nature of the PTO's logic: The PTO in our case, (erroneously) stated that the average artisan (page 35:) "would have recognized how to practice the claimed invention" including a subpopulation. If the PTO's logic would be true this applicant could claim the following bizarre statement that would prevent any future invention for the same reason: *"Any two substances given together could be used for any illnesses. – Chemistry books on known substances and methods of how to make new substances are incorporated herein as reference, as well as ICD codes for a list of all medical illnesses"*. Isn't that what the **WO 02/053140 A2 (page 14 lines 30-33, and page 15 lines 1-2)** application was doing? They have listed 2 compounds, and incorporated all DSM codes for reference to include all mental illnesses without enablement. Thus with the same token and relying on the PTO's logic; a statement of "any methods to make two compounds" could be also incorporated as a reference. That would successfully prevent any patents for a medicament if one would follow the PTO's unconvincing line of reasoning. This PTO logic is absolutely erroneous! This is why the law also asks for disclosure and enabling. Nothing from this above absurd example or from Faour, Chappell or Tollefson or even from the **WO 02/053140 A2 (page 14 lines 30-33, and page 15 lines 1-2)** references would allow the clinician to follow and practice our invention!

The PTO examiner (also) errs of calling a mere mentioning of the broad diagnostic categories (depression) – or the very broad diagnostic categories (mental illnesses) – as "given the disclosure" (e.g. on page 35). The applicant points out that a mere mentioning of a broad diagnostic category or of very broad diagnostic categories is not a sufficient disclosure to enable to practice our invention. The reasons were already given above of why

skipping certain clinical steps is not permissible. Figures 1 and 2, further elaborates on our reply to the first office action.

We state it again that:
Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 201 also notes that: "even if an act or document constitutes prior art under Sec.102, it will not bar patentability of [our] claims unless it anticipates [our] claims. ... **Anticipation only occurs if the prior art reference [is] teaching each and every element of our claims.** If [we] are successful in arguing [- and we think we gave more than enough evidence for that-] that **the reference does not anticipate [our] claims (because it is distinguishable), [we] will be removed that reference as 102(a) prior art bar to the patentability of [our] invention.**"

In re Donohue, 766 F.2d 531 [Fed. Cir.1985]. "A disclosure is non-enabling if it fails to place the subject matter of the claims within the possession of the public..."

As we have shown the prior arts cited do not anticipate our claims. We have also shown the secondary factors that the prior art teaches away.

The same reference by Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) discussing obviousness (35 U.S.C. Sec. 103(a)) at page 219 states (referring to MPEP Sec. 706.02(J).) "that references must ... suggest [our] claimed invention, or [the] examiner must present a convincing line of reasoning as to why the artisan would have found [our] claimed invention to have been obvious in light of the teachings of the references. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." We have shown in our prior and extensive reply why the thinking pattern of one skilled in the art would have been different from the examiner's reasoning, and why one skilled in the art could not have disregarded the boundaries of standard of care without adequate guidance, and without going through a risk/benefit/side effect, available alternatives analysis (etc).

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 220 also states, that: "The prior art reference ... must teach or suggest all [our] claim limitations." **As we have shown it previously (including the secondary factors) that this is also not the case.**

The anticipation did not occur as it was the PTO and not the cited prior art references that came up with the "explanation that was based on unconvincing line of reasoning (false logic)" leading the clinician to commit malpractice by skipping required steps. For these exact same reasons of skipping steps the prior art references did not teach each and every element of our claims! We on the other hand came up with new inventive steps that enabled to use our invention. Since the PTO's presupposition and "false logic" would lead the artisan to commit malpractice the PTO did not present a convincing line of reasoning for obviousness, and therefore the rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985)." (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 219).

The artisan would also need solid reasons for overcoming the strong teaching away and discouraging of using the combnation therapy for the purpose of our claims (and such disclosures were not given by any of the cited prior art or the PTO). "A reference teaches away when a person of ordinary skill, upon reading the reference, would be lead in a direction divergent from the path that was taken by the applicant. (In re Gurley, 27 F.3d 551 [Fed. Cir. 1994].) (Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 224).

Rogers JL (The Complete Patent BookSphinx Publishing Napervile, IL 2003) at page 222 teaches that in overcoming rejection based on obviousness, we can argue (and in our prior reply I think there is no doubt that

we successfully did that) that "the combined teaching of the cited **references still fail to fully *teach the* invention recited herein**". At page 223 it sates: "**If the references are not each directed toward solving the same problem to which the invention is also directed, then the rejection should be withdrawn**. (In re Rouffet, 149 F.3d 1350 (Fed. Cir.1998).)

The PTO have ignored these cited references, the cited law, and our arguments.

> The PTO merely repeated their erroneous logic. The PTO did not reply to our argument of on what basis would that general statement be true and without guidance be a sufficient disclosure overriding the accepted clinical norm and rules. How could the PTO force a clinician to skip mandated steps and to commit malpractice? How could the PTO assume that the average artisan would want to do that?

Very important:

Another line of reasoning would also show of why the artisans and the authors of all of the cited prior art (patent) documents were not in the possession of our invention:

1) All these cited prior art (patent) documents were from big pharma and they would have the financial interest to pursue as many coverage (including our new use) would they been in the possession of our invention. If they were, they would have also no problem of providing the same disclosure and guidance that we did. They failed to do so. Therefore the big pharma prior art or the average skilled in the art was not in the possession of our invention and could not have followed the PTO's line of argument that was not convincing also for the reasons mentioned above.
2) The third requirement of the USC Title 35, Sec 112 (1) is the best mode requirement, which does not permit inventors to disclose only what they know to be their second best embodiment. In other words if they would have known a preferred way of using their invention they couldn't conceal this from the public. (The complete patent book page 25). Giving an extremely wide diagnostic category would be therefore in conflict of the patentability for that reason, would these documents really imply any other use that was already known in the art.
3) Giving an extremely wide diagnostic category [depression or all of the mental illnesses] (specifically **when enablement are very different for some of the subcategories** requiring additional (and non-disclosed **steps** by these prior art documents) would also show that the prior art (and the artisan) was not aware for that use. They could not have substituted these prior art documents for the purposes of our claims. The enablement are very different for some of the subcategories (like non-TRD and non-psychotic depression or as initial treatment for substantially all of said patients) requiring additional (and non-disclosed steps by these prior art documents).
4) The same applies to the low dose concept: Giving an extremely wide dose range as "preferred" application cannot be explained by the PTO as a low dose, or the low dose concept, especially when we have pointed out that Tollefson for olanzapine included a preferred **dose range which is 33% larger than the highest PDR approved dose**. This cannot include the low dose concept –as we defined – of usually being 1/3rd of the dose given for psychosis! Tollefson (or the prior art)'s best mode therefore was not disclosed in sufficient detail to allow one skilled in the art to practice it (Fonar Corp. v. General Electric Co., 107 F.3d 1543 [Fed. Cir. 1997]. The complete patent book page 25.) As we also pointed out the Tollefson (and prior art) reference(s) are for a different use (and or patient population). In addition as we have discussed at page 12-13 [under 10d)] high doses of the atypical medication have an – treatment emergent side effect – which is opposite of the intended use described in our claims.

(See also Reply R).

It becomes evident that the **PTO examiner is not a clinician.**

We also would like to give an analogy to show that the PTO's line of reasoning is not convincing as regards to Chappell (but also for Tollefson, Faour, **WO 02/053140 A2** (page 14 lines 30-33, and page 15 lines 1-2) application, and any similar publications). Our clinical reasoning in this matter is more precise than the following general analogy, never the less it is worth mentioning:
If the PTO thinks that a mere mentioning of a broader group would render another invention – with new indication and new steps – obvious, than a patent in the steam engine area to propel a vehicle would have prevented the patent to propel an aircraft with a jet engine. (An aircraft would fall into the broader category of a vehicle, and the engine in the steam engine area would include the jet engine). The error lies in that, there are additional steps required to be overcome the obstacles for the aircraft and that was not described and enabled in the prior art.

Our specific arguments about the need of **extra steps** in order to use our invention for a subgroup of a wider group are much more convincing than the above example. We have also shown of why the PTO's line of reasoning is not convincing, therefore the rejection should be withdrawn. (Ex part Clapp, 227 U.S.P.Q. 972 (Bd. Pat App. & Inter. 1985).

- 2nd reply **#5);** The PTO did not reply to our repeated questions and arguments about the Tollefson reference (e.g. Reply-26) regarding their statement that: "another embodiment is a method of providing rapid onset treatment of depression to a patient, (p. 2, lines 10-13) **which is drawn to cases which have not demonstrated treatment resistance." (???)**

> After the first office action **I Faxed to the PTO a question,** (on 10-12-06 9:05pm) then not receiving a reply I called (on 10-13-06) the PTO examiner asking on what he meant on that afformentioned statement as that conclusion is not in the Tollefson reference. The PTO examiner has stated that he will call me back with that. He never did, but he did call my attorney representing me at that time. However, as per my attorney, the PTO examiner did not make any explanation on that issue whatsoever. My attorney said **if the PTO would have any such information that is not in the prior art reference they would have to come forward with that**. **The PTO did not do that**! Instead ...

The PTO ignored our argument and statement that the Tollefson reference does not have any such information disclosed on non-TRD cases that the PTO falsely claims that they have. The PTO repeated the same (false) argument in their second office action. (page 26 lines 2-4).

Going into a theoretical case that even if they would have disclosed and discussed a research study involving non-treatment resistant patients they would still have to go through an analysis that we went trough that why the benefit of the group would substantiate to override the currently used and know risk benefit analysis. We have quoted from our provisional application:

> **"One could speculate that if using the SSRI-atypical neuroleptic combination would increase the response rate of treatment-resistant depression, then the percentage rate for improvement would be also higher if given for everybody who is clinically depressed, that is without separating the 'responders' from the 'non-responders'.**
>
> This speculation is probably correct, **but by itself would not substantiate the added risk using the neuroleptics.** With this rationale, the two step strategy would seem still to be the logical step, to treat the depressed patients with antidepressants first, and reserve other strategies for the treatment-resistant group only. In the argument to consider, or start using the combination treatment right

away in all those who are clinically depressed, **it is the decrease of suicide rate that is the paramount important factor**. ..."

So they would have needed to go trough a risk benefit analysis in this regard even if they would have had patients disclosed in their trial with non-treatment resistant depression. None of those conditioned ifs were there however in the Tollefson reference(s).

We on the other hand did provide these steps and enablement. **Deviating from the standard of care or not doing risk benefit alternative analysis is an automatic malpractice as it is also known in the risk management field within the medical art**. The above mentioned document therefore could not anticipate our invention, and in fact **there were inventive and additional steps involved**.

In addition, as we have shown under 2); that Tollefson's combination therapy for TRD when compared to monotherapy published by the same author or compared to other even faster acting monotherapy alternatives, the said and supposedly "rapid onset" was never substantiated even for the TRD!

- 2nd reply **#6a);** was moved above - 2nd reply **#17);** for continuity.

(see also #14-15.)
Please also see #16-18 as an integral part of this argument.

- 2nd reply **#7a);** We would overcome the PTO's argument on the issue of prevention to amend the claims and change the wording to resisting.

- 2nd reply **#8);** The PTO also disregards inventive steps, and falsely states that some claim limitations are **only "various motivations"**. **(page 5 line 8, and page 27-28 lines)**

1) The risk benefit/alternative analysis is just as much of a step that the clinician has to make than the steps diagnosing depression, that is that whether certain symptoms are present or not.
2) The benefit of the group is a well described and defined term, and an inventive step with supporting arguments and enablement. [See page 4-5, Guidance 2a) of the reply to the 1st office action]. That step changes the clinician's decision making process just as much as the risk/benefit analysis or the diagnostic symptoms and diagnostic steps do! These are not "only various motivations"! These are clinical decision making steps toward using or not using the treatment in our invention. In fact, these decision making steps even make our invention as the first choice of treatment, and changing the standard of care. The lack of use of our invention and these inventive steps by others for over 5 years also supports our argument as secondary factors (which were totally ignored by the PTO). The PTO on another line of argument at page 17 has specifically acknowledged that "diagnosis and determination of the best course of treatment" consists of steps! Therefore the PTO examiners contradict with themselves when they deny our claims based on calling these steps as "various motivations".

   With the same PTO logic inventions with prenatal vitamin to resist cleft plate, or aspirin to resist myocardial infarction and decrease the epidemic of heart attacks would not be steps that clinicians would need to make but mere "various motivations", and thus – as per the PTO – similarly unpatentable. That would discourage a great number of inventions for the benefit of the mankind.

   There are many ways (inventions) to use gasoline, you could burn it to heat your house, and you could propel an automotive with it. As per the PTO these (past) innovations would

not be inventions but only various motivations to use the gasoline. This would be against of what the mission of the PTO is that is to encourage new inventions and protect the inventors!

- 2nd reply #9); We will overcome the PTO's misinterpretation at page 13 by amending our claims and using "substantially all of said patients".

The PTO at page 13 misinterpreted the meaning of "treating substantially all patients" in drastic contrast to our specifications reentered from the provisional application under Guidance 2a) page 4 of the reply to the 1st office action, and also is in contrast in the context of the neighboring claims. The PTO consequently errs with his conclusions and ruling.

At the phone interview the PTO also acknowledged (with a sight of relief) **that "of said patients" would render a different meaning.**

The same applies to the PTO's new matter argument on page 14-19, as we intended not claiming substantially all patients in an independent, but in the dependent claims intending to limit the type of patients described in claims 1, and 2 for example.

Figure 3 spells it out in a graphical form of what we were teaching in our provisional, utility applications and in our 1st reply about Guidance 2a).

The "benefit...for the group of patients / benefit for a group" was described at page 4 lines 15-16 & 36 in Guidance 2a) of the reply to the 1st office action, re-entered from the provisional application.

The meaning of substantially all of said patients was described as "we are following similar procedures and give [compound] routinely for everybody" and "start using the combination treatment right away in all those who are clinically depressed" at page 4 lines 29 and page 5 line 9 in Guidance 2a) of the reply to the 1st office action, re-entered from the provisional application.

Both instances were reentered from the provisional application [along with Guidance 2a) of the reply to the 1st office action]. These terms therefore were not new matter and were described in the specification.

Figure 3.: Graphical example #3 of the unconvincing line of reasoning by the examiner, of not understanding the importance of "substantially all of said patients" (within the group of patients described in independent claims 1, 2; that is within non-TRD, and non-psychotic depression). The examiner also misinterprets the term "benefit of the group":

PTO: In Figure 1 and Figure 2 we had shown of why the PTO's logic to use A+B couldn't be followed by the clinicians without the artisan committing malpractice. So at the time of our invention – as strong secondary factors also show – the clinicians had to follow the steps below not only for the individual patients but even more for "substantially all of said patients" or "all patients" within the non-TRD and non-psychotic depression and in particular if it is for initial treatment:

A+B as initial Rx for "substantially all" or "all patients" (within the claim 1, and 2, that is for non-treatment resistant, non-psychotic patients) ----------→ **(Clinicians** at the time of our invention and in doing the required steps of Figure 1 and Figure 2,)

End result----------→ do not use it (A+B)

However, also as the secondary factors show the clinicians were still skipping steps like the "benefit of the group analysis" that we have shown being an important and crucial step that drastically changes the clinical decision for the benefit of the group and the individual, and thus changes the standard of care and first choice of treatment.

versus (see also Guidance 2a) and b) in our reply to the first office action, specification re-entered from the provisional application)

My invention and teaching is recognizing and is adding additional steps:
A+B as initial Rx for substantially all or all patients (within the claim 1,2, that is for non-treatment resistant, non-psychotic patients for the benefit of the group) --→ (black box with additional steps) ----------→ **do use A+B**

The group of substantially all or all patients (within the claim 1,2, that is for non-treatment resistant, non-psychotic patients) and as for initial treatment with A+B:

Step one:
We do not know that who in the group would be suicidal, therefore another risk/benefit/alternative analysis should be performed: The analysis is on the risk of giving the medication combination versus not giving it. We need to ask:
When would more death occur?
Since we do not know who in the group would be affected therefore the benefit of the group is also for the benefit of the individual. ----------
----------→ **do use A+B**
(The analysis is similar to our appendicitis risk benefit analysis that is known to the art and what we have specifically described in our provisional application).

Step two:
Compare this decision to other practices within the standard of care:
Compare the Suicide risk of MDD to the actual suicide risk of Borderline personality disorder (BPD), where the same combination is given and where it is an accepted method within the standard of care. [see Guidance 2b) in our reply to the first office action] Since the completed suicide rate is significantly higher in MDD than in BPD and since other enablement (reasons) were given, the justification to use A+B is clinically there with absolute clarity. ----------→ **do use A+B**

- 2nd reply **#10);** The PTO also errs on page 14 "new matter" with respect to claim 65. It has to be noted, that initially my own attorney (at that time) also had the same concern, but after my reasons he accepted that I was right and therefore that claim was left in: My argument was that active metabolite is a logical and inherent step just like the example in the following analogy: If you invent "that grape is good for some illnesses, than grape juice would be also included in that, since when you eat a grape and ground it with your teeth you would make grape juice". In the same way the human body makes an active metabolite of risperidone, therefore it is inherent and not a new matter! (We hereby request the PTO's decision to reverse of that being a new matter.)

At the phone interview (post 2nd OA) the PTO stated that they would not accept that reasoning because of possible differences of pharmacokinetics (without saying what difference). We traverse that general reasoning. (However, we said that if our other claims are allowed it seems that it would not worth for us fighting over that issue).

- 2nd reply **#11);** The **PTO in the 2nd and final OA ignored all the strong supporting secondary factors, that we specifically listed in great details in the reply to the 1st OA (pages 93-99).** We specifically refer back to the reply to the 1st OA.

At the phone interview the PTO remarked that it is well established that others not using an invention [that is the invention of the prior art listed by the PTO and applied and interpreted as being obvious to our claims] does not makes an application [ours] patentable. We traverse this line of reasoning being convincing as relates to our application (see later). However, the PTO also showed an interest and acknowledged that secondary factors can have a value in the evaluation.
(please also see in the enclosure:

1a) Secondary factors in determining unobviousness. From Patent attorney David Pressman, Book: "Patent it yourself". Nolo, 2004 10th edition, pages 5/19- 5/22.

1b) General arguments against obviousness. From Patent attorney David Pressman, Book: "Patent it yourself". Nolo, 2004 10th edition, pages 13/25-13/16.)

E.g.:

1) **Previous failure of others** (See e.g. FDA directors' inability to give adequate solution – see inserts in reply to the 1st OA; suicide and antidepressant emergent suicidal ideation/suicide remains an unsolved problem)
2) **Solves insoluble problem** (See e.g. FDA directors' inability to give adequate solution; overcoming the strong teaching against with new risk/benefit/alternative analysis for the benefit of the group)
3) **The invention is in a crowded art** (There are a lot of inventions on antidepressants)
4) **Unsuggested modification** (e.g. for initial treatment substantially in everybody depressed; treatment of 1st choice; looking the interest of a group; lower dose of antipsychotics; etc)
5) **Unappreciated advantage** (for the paradoxical effect of antidepressant worsening depression; for the development of tolerance against the antidepressants; for antidepressants causing suicide; modifying course of illness, resisting SI ["prevention"] etc)
6) **Solution of long felt and unsolved need** (not solved by others) (e.g.resisting SI ["prevention"]); (See FDA director's inability to give adequate solution; see Tollefson / Eli Lilly and Chappell / Pfizer not recognizing the use for preventing the paradoxical effect of antidepressants worsening depression or causing suicide; and not speaking up in the midst of FDA and media attention.)

7) **Contrary to prior art teaching** (even in the light of intense media attention, and highly recognized experts like FDA chiefs; See Texas algorithm and others including NIMH sponsored studies) Contrarian invention,

8) **Synergism** (described in the application, and no prior art disclosed our description)

9) **Prior art references would not operate in combination** [inoperative combination] (low dose of antipsychotic is critical and essential – higher dose can cause the opposite, the treatment emergent unwanted effect [worsening of depression (depressogenic effect), treatment emergent anxiety, akathisia – linked to suicidality]; initial treatment for the interest of a group is essential;)

10) **References teach away from combining** (or its use) for non-TRD, non-bipolar depression [see Texas algorithm and others including NIMH sponsored studies]).

11) Therefore we have **unexpected results.**

12) **Unrecognized problem** at the time of our invention of the paradoxical effect of antidepressants causing suicide – at least by the majority of psychiatrists and the FDA.

13) **Lack of implementation over 5 years later** – even in the intense media attention.

14) **New principle of operation** - The invention is utilizes a new principle of operation. The applicant has blazed a trail, rather than followed one. (The reasons of using the antipsychotics, how even the "extended" non-DSM depressive symptom has an effect on other symptoms and the depression as a whole, and providing synergistic effect through each target point of these extended non-DSM, or depressive DSM symptoms, of how the psychological, medication and [gene expression] effects interact; of using the invention for the benefit of the group, new risk/benefit/alternative analysis – enabling and necessitating the use of the invention as a first choice of treatment and in substantially all (of said) patients, effect on cognitive distortion).

15) **Inability of competitors** - Competitors ("big pharma") could not claim and/or enable our new use invention despite of the long felt unsolved need, and even after more than five years later there is an inability – as exemplified e.g. by the FDA directors perplexing on the problem. In addition – as disclosed in various parts of our arguments and in page 27 (Another line of reasoning) – none of the prior art documents were in the possession of our invention.

16) **Solved a different problem** (than the cited prior art references – and we have enabled the solution to the problem).

17) **No convincing reasoning** The examiner has not presented a convincing line of reasoning as to why the claimed subject matter as a whole, including the differences over the prior art, would have been obvious. [The PTO line of reasoning would have lead to malpractice by skipping mandated risk/benefit/alternatives steps; The PTO line of reasoning was unconvincing as it deviated from the standard of care; The tenets of the PTO did not withstand scrutiny, (on Tollefson showing a rapid onset action for non-TRD – over antidepressant (SSRI) monotherapy or over other antidepressant monotherapy alternatives – and **that tenets of the PTO was never substantiated** or shown by the PTO)]. In addition, the PTO did not check for secondary factors before coming up with any of their unconvincing line of reasoning.

18) **Modifications necessary** It would have been necessary to make modifications, not taught in the prior art, in order to combine the references in the manner suggested. (new risk/benefit/alternative analysis – for the benefit of the group – and comparing the current standard of care with new information presented (on BPD versus MDD), thus enabling and necessitating the use of the invention as a first choice of treatment in substantially all patients; low dose of antipsychotic is critical and essential – higher dose can cause the opposite, the treatment emergent unwanted effect [worsening of depression (depressogenic effect), treatment emergent anxiety, akathisia – linked to suicidality]; initial treatment for the interest of a group is essential; enablement through the reasons of using the antipsychotics, and how even the

"extended" non-DSM depressive symptom has an effect on other symptoms and the depression as a whole, and providing synergistic effect through each target point of these extended non-DSM, or depressive DSM symptoms, of how the psychological, medication and [gene expression] effects interact; effect on cognitive distortion; using the method for other new use (treating paradoxical effect of antidepressant worsening of depression and causing suicide, treating residual symptoms of depression, etc).

19) **Claimed features lacking.** Even if combined, the references would not meet the claims.

20) **Multiplicity of steps required** New steps are required to enable and use our invention (new risk/benefit/alternative analysis – for the benefit of the group; low dose; enablement [see above]; ; effect on cognitive distortion; recognizing problem of paradoxical effect of antidepressant worsening of depression to coming up with solution for resisting suicide).

21) **Multiplicity of references.** Even large number (3) of references would not render the invention obvious due to the new steps, modifications, new use, enablement and other reasons (e.g. Prior art references would not operate in combination [low dose]; as shown at page 27 "another line of reasoning" the authors of the cited prior art were not in the possession of our invention).

If the value of the secondary factors could be brushed off by a statement that others not using an invention [that is the invention of the prior art listed by the PTO and applied and interpreted as being obvious to our claims] does not mean patentability [for our claims] [of overcoming obviousness rejection], than these exact same secondary factors would not have been created by court(s) and by the PTO guidelines, (since they would have no value). In fact, and in our case the opposite is true. Since a great number of secondary factors apply to our invention, together these support the novelty and un-obviousness. This is specifically true and is **intensified** in light of the intense media attention and potential legal liabilities of not coming forward and/or using the invention by the same companies that were cited against the applicant as "prior art". In addition at page 27 under the section of ("Another line of reasoning" would also show of why the artisans and **the authors of all of the cited prior art (patent) documents were not in the possession of our invention**). We described several other factors of why the authors of prior art were not in the possession of our method. Therefore all that, and the secondary factors together with our other arguments **clearly shows that the prior art is distinguishable** and the obviousness rejection should be withdrawn. Therefore at least substantially most of our claims should be allowed for issuance.

- 2nd reply **#12); and #13);** [The phone interview gave a solution to these items]. The PTO also ignored in the 2nd OA the applicant's request of parts of the provisional application be reentered to the utility. The PTO also ignored the applicant's request for help as to potentially include additional parts from the provisional (like the ones pasted to the reply to the 1st office action). However, at the phone interview (that was granted for after the 2nd OA) the **PTO said that the applicant would be entitled to re-enter specification from the provisional** and said that grammatical changes would be allowed. The applicant said that he would paste the parts from the provisional, mark for the PTO where it came from (so to be exact), and that he would clearly mark grammatical changes by crossing out and putting correction in [squared parenthesis], in addition to making note to the PTO about that. In this way to the applicant's best knowledge the re-entered parts contain no new matter. It is further notable that to the applicant's knowledge the whole provisional application was published by the PTO and made available to the public (or at least to patent attorneys/applicants).

We are also enclosing the original (unchanged) copy of the submitted provisional application (since the formatting was changed in the published PTO version (possibly as a result of scanning or clearing bold and underlined parts). In the published version of the provisional (by the PTO) the bulletting - and with

it - the separation to new paragraphs of certain reasoning were not carried over diluting or jeopardizing clarity of our guidance (e.g. as regards to our theory/reasons to use of the antipsychotic). It is of note that the same copy was also submitted to the US copyright Office following the PTO submission.

- 2nd reply **#14);** PTO regulation MPEP Sec 707.07 (j) specifically require patent examiners to help inventors pro se (no lawyer) cases. (See also pages 1/2 and 13/43 of D. Pressman "Patent it yourself" Nolo 2004.) The IACtr [IAP]/(PTO) also said that on 12-1-06 ref#1-55698886. The PTO examiner was aware that the applicant was going through a process of his PTO registered patent attorney abandoning him, as that fact became evident from the applicant's fax to the PTO which Faxed letter noted that the attorney did not notify the applicant of the office action for about two months. In addition the enclosures of the reply to the 1st office action clearly stated that the applicant have lost his attorney representation (revocation of the power of attorney). So the help from the PTO examiner was expected – and even asked, but ignored.

It is also of note, that the PTO's list of vast number of registered patent attorneys is of little help to the applicant since the field of expertise and the undergraduate specialty is not listed at the PTO's web page. (You wouldn't want to have a brain surgery performed by an internist or a proctologist, and the same way an engineer patent attorney would have no knowledge of psychiatry. This applicant has find out on his own experience, that some patent attorneys would not even know the difference between an antipsychotic and an antidepressant.) Also, as media news has brought up to light the concern in regard of conflicts of interest and the "effects" of big pharma's money on the FDA; similarly concerns can also be reasonably raised with the PTO, as another governmental agency. (See enclosed copy of "FDA loosing credibility with public, own staff. Clinical Psychiatry News 34:12 December 2006, page 67). In addition, qualified patent attorneys in the applicable field – if one can find them – who are familiar with psychopharmacology and psychiatry, are likely to work at one point for "big pharma" which raises the issue of conflict of interest in helping small entity inventors against the big pharma's multi-billion dollar interest. (As it turned out recently, even the attorney firm that filed my utility had a major contract with "big pharma" representing them in a class action law suit).

The applicant continued effort in search for a registered patent attorney with appropriate undergraduate knowledge in the field has failed. (His other two attorneys from the Webb law firm in regards to this applicant's other pending application, have left that firm (and as it turned out to the applicant's knowledge these attorneys also have worked for "big pharma" even at the same time as they filed the application.) The applicant's former attorney (Deb Anderson) who filed both of the applicant's utility applications has specifically declined any future help and representation. In his continued search for a qualified patent attorney in the applicable field, this applicant has gotten only rejections from patent attorneys and reason of conflict of interest from big pharma. **It can be expected that any good and competent patent attorney with that specific skill, (or their law firm), would have been hired by "big pharma". There are not many independent inventors to support patent attorneys with this specific pharmaceutical/psychiatry skill, with the understanding that most often expensive research studies are also needed for the PTO which are usually beyond the reach of the independent small entity inventors. So the expectation to find a competent attorney in that field who refuses to work for "big pharma" and can survive only on assisting small entity inventors without conflict of interest is nil to nothing.**

So, the PTO regulation on the PTO to help an applicant if not represented by an attorney would need to be applied with an increased weight.

The applicant must strongly rely on the PTO's specific and explicit help, especially with the claim language to assure maximum patentability. Enclosure 1c) A14 (see pages 3 and 16 of this reply) specifically spells out – in contrast to the PTO's statement at the interview – that the PTO has to give assistance in claim drafting, as set for by the PTO regulation.

- 2nd reply **#15);** The applicant on the last page of the reply to the first office action **specifically requested that if any of the claims would not be accepted he would like a meeting with the examiner**, and the PTO specifically failed to comply with this request.

The applicant's such request was in accordance with the advice of Rogers JL The Complete Patent BookSphinx Publishing Napervile, IL 2003 page 160.

The applicant also called the PTO help desk **(ref# and date 10-26-06 1-49470302, and also 11-30-06 ref#: 1-55521338)** and there the PTO also said that the PTO should honor this request about the interview and they have to set up an interview. The applicant's attorney (before the applicant lost his representation also said the same that the PTO should grant such a meeting, and it is customary to use that language for that request that we are using in our reply to the 1st OA). The 2nd and final OA issued without an interview.

A phone interview was only granted after the 2nd OA. The senior examiner was not present, and the PTO stated that he is only a "junior examiner" and is not allowed to withdraw any arguments, therefore for substantial part the interview was one sided where only the applicant provided information to the PTO. The IAP/PTO suggested to call the supervisor and ask her to review the case and allow an interview with her. I did that on 7/22/07 and my request was denied/not granted. The supervisor said that the junior examiner is a good examiner, and that they feel that they have a firm case for the rejection. However the PTO agreed to have an interview with the applicant after his written reply (planed RCE at the PTO/IAP's suggestion) and have that interview before further written action.

If the interview that was requested in the reply to the 1st OA would have been promptly granted this reply would be still before the 2nd and final OA and not as an RCE.

- 2nd reply **#16);** At the phone interview (as mentioned before) the applicant's theory or reason were no longer find non-existent or irrelevant. However, as to the written part of the 2nd OA it is submitted that the applicant's theory or reasons that he provided are relevant.

The PTO disregarded our response to the 1st OA of drawing attention that indeed we have provided a theory or better yet reasons of why atypical antipsychotics (either alone or in combination) may target and be useful for the treatment and prevention of depression and suicide. (Reply 6 and Appendix A, B, C of reply to the 1st office action). The PTO just kept repeating that we have not provided a theory (for example at page 6 line 21 in the second office action), and the PTO continued to make further conclusions with disregarding the facts and thus erroneously supporting their own view of the art being unpredictable and undeveloped.

Although after making several false conclusions the PTO came back (on page 10) and addressed simply with a pure statement and no counterargument that the theory provided was not relevant. The PTO did not provide any support whatsoever to this statement. (The argument at another place in regards to the functional language used, would not apply here, since in our theory or reasoning we have specifically showed enablement for the class of drugs.)

The theory and proofs provided did not limit our invention to currently known drugs, but a class of drugs. See for example Appendix A of reply to 1st OA: In particular, in Appendix A: #B) we specifically made arguments of how cognitive distortions in the depressed individuals overlap with thought disorder, and thus for the skilled in the art that partially – and only partially – would support using the class of drug called antipsychotics together with our additional enablement. We also had several other supportive arguments that together were absolutely convincing. There is known definition and tests available to clearly demark that class of drug, so it is not indefinite. (We have discussed that with reference to "big pharma" under 2nd reply #6) [moved to above #17 for continuity]. Never the less **we amended** our claims 1-3 and 109-118 to reflect the guidance from the PTO.

The PTO errs on the logic that the claim language encompasses infinite number of drugs that require testing. We did not claim infinite number of unknown substances, but a class of drugs, andtipsychotics and antidepressants. Both classes are well defined just as SSRI's are, that the PTO states (on page 10 line 8) that we should have used as a language. There are just as accepted tests to demark this two classes of drugs then there is for demarking the group of SSRIs. There are also many unknown substances that would be SSRI but not invented (or discovered) yet.

> Yet as shown earlier **EP 0966967 A2 page 3 [0012] lines 18-21)** and **EP 0958824 A2 (page 14)** patent applications submitted by a major pharmaceutical company also claims SSRI and atypical antipsychotic. You can expect that they and their attorney's know what they are doing. The PTO did suggested this applicant in the 2nd OA to use such a language. Hence, the claims were amended to reflect that. [We are discussing that under #6) that was moved to above #17 for continuity].

Guidance 2b and Appendix A: #B) in our 1st reply further provides other reasons and rational - independent of currently known drugs, and is referring to the class of drug antipsychotic and atypical antipsychotic. It lists (among others) our reasons including our discovery to see non-psychotic depression also as a thought disorder. In Appendix A: #B) we also stated: "It seems however, that there is an overlap between the cognitive distortions; the "mini psychosis" of BPD; and the "full blown psychosis" of psychotics; all of them being out of touch with reality but in different degrees." Our discovery that other than the DSM symptoms should be systematically relied upon in depression testing, as well as that by pharmacologically addressing one depression symptom improvement in another can be expected, and discovering of how that would work psychologically and correspondingly biologically through clinical neuroplasticity [and gene expression changes] was a synthesis never done before. All this with our other guidance provided enablement and changed decision making steps.

#6a); was moved here to right above "- 2nd reply #17);" for continuity:

moved - 2nd reply #6a); In regard of **#6a) - #6e)** we have **amended our claims** to change claim language reflecting the PTO's suggestion. However, we have defined (and the prior art have defined) the term "**newer antidepressants**" (e.g. page 11 lines 30-33, of the utility). "As used herein, the term "newer antidepressants" is used as that term is understood in the art, and generally refers to

antidepressants excluding traditional tricyclic or tetracyclic antidepressants and excluding MAO (permanent inhibitor)." The term antidepressant and antipsychotic is also defined in the prior art. We have even made reference to articles and authors that defined various antidepressant groups (e.g.:Thase, 2000, Willner P. 1997, Heresco-Levy, U. 1998,). These definitions are beyond just a functional description. We also gave a list of newer antidepressant examples. Therefore the term as used in our claims are not infinite.

moved - 2nd reply #6 b); We have defined (and the prior art have defined) the term "**atypical antipsychotics**" (e.g. page 13 lines 5-27 of the utility, and we have also provided a list of examples. The term antipsychotic is also defined in the prior art. These terms are well demarked and not infinite as it is also further explained below. The term atypical antipsychotic is understood in the art and that term is disclosed. We went beyond functional description (e.g. beyond the description of the less TD side effects). We disclosed that the most powerful predictor of atypicality is fast dissociation from D2 receptor. (Kapur, S et al 2001). (...and at the same place description for the historical research for [typical] antipsychotics with high affinity for the D2 receptor or strong binding to dopamine receptor was also disclosed.) Therefore the term as used in our claims are not infinite.

moved - 2nd reply #6c); the PTO examiner also acknowledged that in the Chappel reference "a **D4 receptor antagonist, (an antipsychotic)" was used (see e.g. p 33 of second office action)** in the prior art reference which is an antipsychotic, so the PTO has some knowledge on antipsychotics and that the antipsychotics are a well defined group just like SSRIs are. We submit that these terms are not infinite for these reasons. The requirement or of the PTO statement that "it is not possible to predict the efficacy of any particular antipsychotic" therefore is incorrect. We specifically draw attention to the fact that these terms are defined, and also that we had been giving adequate guidance as for these classes of drugs, and therefore we have enabled the one skilled in the art to practice our invention.).

Now, Elli Lilly (Tollefson) in their patent application (see **EP 0966967 A2 page 3 [0012] lines 18-21)** states the definition of SSRI and that there are known tests to determine an SSRI. They even made statement that there will be in the future new compounds discovered that would prove to be an SSRI. Yet in their claim 1, they used the term SSRI and atypical antipsychotic. The same applies to e.g. claim 1, of **EP 0958824 A2 (page 14)** (by the same company and inventor). – As a matter of fact **even the PTO specifically suggests for the solution for us to use a functional language "such as serotonin reuptake inhibitors [SSRI],** dopamine system stabilizers, and the like" (page 10, lines 7-9 of the 2nd office action). The terms we have used are just as well defined as the SSRIs, and for the antidepressant and antipsychotic terms we have used as well as for the SSRIs there are existing and available tests. So that particular functional language is allowed and used in the "big pharma" patent – also with the approval of their expert attorneys. **We made an attempt to correct the "functional language" in our claims (1-3, and 109-118** relying on the PTO's specific suggestion in the OA) and we are still relying on help from PTO as regards to claim language to ensure maximum patentability.

moved - 2nd reply #6d); Most importantly, in regard to of the PTO statement that "it is not possible to predict the efficacy of any particular antipsychotic" the following should be noted:

It is obvious to treat depression with an antidepressant and that does not need enablement.
(The enablement is only to show if a particular new compound is an antidepressant or not. That would be patentable by others and that would not conflict with this application.) If the patent office would ban of using costmary words like chairs or table or objects to sit on in being afraid that somebody would invent a new currently not recognized version of that word, than we would not be able to use the

English (or any language). If somebody invents a new wheal, that would be patentable. However, if it falls within the category of wheal than prior patents on that category still reveal the innovation of that time. The patent holder of the old invention would not be able to use the new invention without permission. These are the general patent principles that the applicant understands from the patent books he read.)
So, as regards to our invention it is obvious to treat depression with an antidepressant and that does not need enablement. Our invention lays in the combination of using antidepressant with an antipsychotic (or antipsychotic alone) for a specified subgroup of depression with additional limitations. The enablement needs to be on the use of antipsychotic (alone or in combination with the newer antidepressants – as we have defined that group). We have amended our claims in regards of the functional language to limit any antipsychotic to the currently known groups of antipsychotic groups.

(However, - and even though that we have amended our claims to comply with the PTO's request - we have to mention that we have enabled the general group of antipsychotics, through our reasoning and theory. That included in part – and only in part – discussion of how the non-psychotic depression that is currently classified a mood and not a thought disorder could be seen as a thought disorder where the antipsychotic medication could be useful (and how the full blown psychosis, the "mini psychosis" of the BPD and the cognitive distortions in our interpretation overlap, as well as a whole other list for enabling the antipsychotics for the purposes of our claim. That included the new view of relying on non-DSM depressive symptoms and on how targeting one depressive symptom can have an effect on the depression in general (synergism). Furthermore, for our enablement the clinical neuroplasticity, the interaction of the psychological, the medication effects and [gene expression effects] were also described as nowhere before. For a full enablement other factors were met like the risk/benefit analysis, and the benefit of the group – all those were not described this way ever before.) So the enablement that we have provided was for the group of antidepressants and antipsychotics, and yes, that included all the current and future agents that meet the definition of being antidepressants and antipsychotics.

In the 1st office action the examiner has stated that:
"Because the terms antidepressant and antipsychotic both encompass a large number of drugs of varying structures and methods of action, and because antipsychotic drugs differ significantly from each other as *disclosed in Applicant's specification, (p. 13, lines 11-15)* **no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally."**

Although, in the next section (#17) we will specifically address that the above was a misquote, the above shows that indeed **any one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally, <u>and that can be done specifically as we have enabled our method through the class of drugs called antidepressants and antipsychotics</u>.** (see "reasons" and other enablement in the specification.)

However, in order to comply with the PTO's requirement, <u>we have amended our claims</u> for both of these classes of medications, and more so for the antipsychotics so that the functional language would be more restrictive.

We were using a more restrictive functional language for the antidepressant:

..."antidepressant, wherein said antidepressant is a newer antidepressant, and wherein said newer antidepressant is defined as an antidepressant excluding tricyclic antidepressants, tetracyclic antidepressants and permanent inhibitors of monoamine oxidase,"... as that was specified in the utility.

For the antipsychotic we were also using a more restrictive functional language:
... "antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer". This was the functional language that the PTO has suggested (e.g. like SSRI and dopamine system stabilizer) in the 2nd OA.

We are convinced that our extensive reasoning would be convincible. However, in order to save time (and assist the PTO in helping us) we have included herein an alternate claim language for "just incase", that is based on the functional language that was in existence in claims 11 and 12, and that had not been criticized as for that particular functional language by the PTO:

Alternate Claim 1. (Currently Amended): A method for treatment of a patient suffering from major depressive disorder, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic.

Alternate Claim 2. (Currently Amended): A method for treatment of a patient suffering from unipolar depression, the said method comprising administering to said patient at a time selected from the group consisting of, as an initial treatment, as soon as possible and upon presentation of said patient to a physician or other health care provider an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer, and wherein said unipolar depression categorized as non-treatment resistant and non-psychotic.

Alternate Claim 3. (Currently Amended): A method for treatment of a non-psychotic patient ~~selected from the group consisting of (a) a patient~~ having cognitive distortions with functional impairment or health hazards~~, wherein said patient is suffering from major depressive disorder, wherein said major depressive disorder categorized as non-treatment resistant and non-psychotic~~, wherein ~~the~~ said method comprising administering to said patient ~~as an initial treatment or as soon as possible, or upon presentation to a physician or a health care provider, or and (b) of a patient undergoing smoking cessation or nicotine withdrawal, the method comprising wherein in either case (a) or (b) the method includes administering to said non psychotic patient~~ an effective amount of an antidepressant, wherein said antidepressant is selected from the group consisting of serotonin reuptake inhibitors, a selective norepinephrine reuptake inhibitors, combined action SSRI/SNRI, serotonin-2 antagonist/reuptake inhibitors, an antidepressant with alpha-2 antagonism plus serotonin-2 and serotonin-3 antagonism, an antidepressant with serotonin/norepinephrine/dopamine reuptake inhibition, an antidepressant with

norepinephrine and dopamine reuptake inhibition, 5-HT-1alpha antagonist, 5-HT-1beta antagonist, 5-HT1A receptor agonists, 5-HT1A receptor agonists and antagonists, 5-HT2 receptor antagonists, viloxazine hydrochloride, dehydroepiandosterone, NMDA receptor antagonists, AMPA receptor potentiators, substance P antagonists/ neurokinin-1 receptor antagonists, nonpeptide Substance P antagonist, neurokinin 2 antagonists, neurokinin 3 antagonists, corticotropin-releasing factor receptor antagonists, antiglucocorticoid medications, glucocorticoid receptor antagonists, cortisol blocking agents, nitric oxide synthesize inhibitors, inhibitors of phosphodiesterase, enkephalinase inhibitors, GABA-A receptor agonists, free radical trapping agents, atypical MAOI's, selective MAOI inhibitors, hormones, folinic acid, leucovorin, tramadol, and tryptophan in combination with an antipsychotic drug, wherein said antipsychotic drug is selected from the group consisting of a typical antipsychotic drug, an atypical antipsychotic drug, and a dopamine system stabilizer~~, and wherein said typical antipsychotic drug is administered at a low dose~~.

We hope that the PTO would be satisfied with our reasoning (that continues) and also with the functional language of the (non-alternate) amended claims 1-3 as is, and we would not have to rely on the "alternate claims 1-3" above.

moved - 2nd reply #6e; We also feel that **the goal and one of the primary mission of the PTO is to encourage new inventions that the society needs,** and that without incentives would have never been conceived or at least not at that time. If the PTO would only allow patents that are so limited that it is very easy to work around, the whole purpose of patent process would loose it's primary mission (to encourage patents). It took over 5 years for the PTO to evaluate this patent and new medications came out to the market since, and more are expected. If patents – that are otherwise enabled for the class of medications – would only be allowed for the currently used medications, at the time of the invention - the above patent office's primary mission could not be lived up to.

See also # 17, (#4-15.)
Please also see #16-18 as an integral part of this argument.

- 2nd reply #17); We have amended our claims to reflect the requested claim language. However, the examiner was misquoting the applicant: We submit that our extensive reply was sufficient to answer the questions raised by the examiner. It became evident that the examiner is not a clinician and is unfamiliar with the clinical thinking:
So therefore we need to draw attention to the following:
In the 1st office action the examiner has stated that:
"Because the terms antidepressant and antipsychotic both encompass a large number of drugs of varying structures and methods of action, and because antipsychotic drugs differ significantly from each other as *disclosed in Applicant's specification, (p. 13, lines 11-15)* no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally."

First of all the above is an incorrect quotation. **The correct quotation (from p. 13, lines 11-15) is**: "The various atypical antipsychotics have a diverse receptor binding profile and they are not only differ from each other but also from the dopamine system stabilizer aripiprazole."

There is a huge difference between the two as in the incorrect quotation the PTO examiner has included his own statements as if we would have stated that.

Second, our main line of reasoning and our enablement was not through that specific line of reasoning, that is of attempting enablement through bringing in various theoretical explanations on the atypical antipsychotic drugs' receptor binding profile as for their use in depression, that is to attempt to speculate a specific antidepressant action that would be similar to the other antidepressants. In fact we have critiqued similar simplistic TV advertisement from "big pharma" of how a simple neurotransmitter deficit and pharmacological replacement theory was "misleading". We described that under the discussion of clinical neuroplasticity and the interaction of medication with psychological [and even gene expression] factors.
Moreover,
a) we have stated in the utility (page 14 lines 7-9) that "The ability of the combination treatment to reduce the risk of suicide may be independent of (or at least not limited to) any action of the antipsychotic medications on mood."
b) we also stated that "The combination of an antidepressant with an antipsychotic, preferably an atypical antipsychotic, is likely to be superior to an augmentation strategy with two antidepressants" (utility page 14 lines 9-11). Our theory (reasoning) on the antipsychotic's action also supports that statement.
Going into a theoretical "what if" scenario, if in the future they would discover an antipsychotic that would also turn out to meeting the criteria for being an SSRI (or any other class of antidepressant) at the same time (as being also an antipsychotic), the risk/benefit analysis – without the guidance that we were giving – would still not allow a mere substitution of that dual action antipsychotic over a regular SSRI (antidepressant) or over other alternatives of combining two antidepressants (like it is done for TRD), unless that particular dual action compound would not have the (life threatening etc) side effect profile associated with the antipsychotic group. There needs to be an enablement for the action other than the receptor binding profile of an antipsychotic if indeed a dual action antipsychotic would be discovered in the future. (This is where the risk/benefit/alternative analysis and the "benefit of the group" that also coincides with the benefit of the individual is crutial.)

Third, **we have provided enablement through the description of the class of medications** that is the antipsychotic and atypical antipsychotic medications for using them alone or in combination with antidepressants for the purposes of our claims. That is the main point in our argument.

Fourth, we have addressed the examiner's argument for example in our reply 6 to the first office action. We were also providing our theory and rational to use these classes of drugs. The PTO disregarded our argument and just repeated itself. And this is exactly our point here.

So in summary of the main point, it is true that we were very detailed in describing the various features of antipsychotic drugs as we wanted to be explicit with the details, (and our real quotation is true)! However, when it came to enablement and giving a theory or rational the average artisan would been able to use our invention based on our guidance without undue experimentation, and use these guidance for the classes of drugs described. We had used and relied on the features of the class of drugs called atypical antipsychotics and/or antipsychotics. Similarly, we were very extensive in explaining

depression and antidepressant effects not only pharmacologically but on the psychological [and even on gene expression] level.

So the PTO examiner errs with that conclusion, and our method is not infinite as it is well described, in addition that we have also met the enablement requirement as for the class of the aforementioned class of drugs. (see also #6 and #16). However, as we mentioned **we amended our claims**.

- 2nd reply **#18);** We have amended our claims to reflect the requested change in the claim language. However, the PTO also errs on demanding a vast number of animal and human experiments from us. Again, the logic that the PTO provides is not substantiated; that is the need to provide enablement with these experiments for any antidepressant and any antipsychotics. **We have enabled our method for the class of drugs. Any ongoing research to find new drugs would only need to be done to see if these new compounds fit the class of antipsychotics or antidepressants. That is irrelevant from this patent's standpoint as here the class of drugs were enabled.** Otherwise the PTO would contradict to their own statement in wanting us to rephrase the functional language of the claims to SSRIs and the like to avoid infinite language. (page 10 lines 7-9). This is exactly what we have argued against above (#6) as there are many SSRIs that are not invented yet. (See also **EP 0966967 A2 page 3 [0012] lines 18-21**). Yet the class is well defined. The experiments to find drugs that fits criteria for being SSRI (or to be within the defined "newer antidepressants" and "atypical antipsychotic" categories) do not need to be done for limiting infiniteness, but merely to see if a new substance meets the criteria to be within that well defined group of SSRI (or the other defined classes of drugs). There is an important difference between the two. The classes of drugs that we have cited are well defined, just as the SSRI's are, therefore there is no need to prove the usefulness of any antipsychotic with any antidepressants, but the usefulness of these classes of drugs. The language used are not infinite, but well defined.

The theory and reasons we have provided (and discussed elsewhere) fits the enablement criteria for the clinician for these classes of drugs, for the ordinary skilled in the art! Therefore we are repeatedly asking to remove the enablement and other rejections and allow issuance for our claims, specifically that we have also **amended** our claims.

> We do not want to over explain things if the above arguments are accepted. However, **the same scrutiny would discourage and substantially disallow many new inventions that our society badly needs** for example in the case of the energy crisis. A new energy or method to propel a vehicle could be disallowed on the same bases of "infinite language" as new vehicles (as category similar to the SSRIs or atypical antipsychotics) could be still invented in the future. Rephrasing the language to propel an object to motion may face the same problems as there may be many new objects (like subatomic particles for sure) that could be and would be still awaiting discovery in the future. **So the PTO would be in contradiction with its main and primary mission statement that is the most important of all, that is to encourage new inventions.**

- 2nd reply **#19);** The PTO in the 2nd office action finally acknowledged that the infinite language and his demands for extensive animal and human experiments and thus the need for enablement requirement would be removed for all currently known drugs used in psychiatry, yet the PTO still did not give allowance to any of the dependent claims where these very specific and currently used drugs were listed.

- 2nd reply **#20);** We had mentioned in our reply to the 1st office action that the PTO cannot claim that our invention is logical just because it seems to be logical to the PTO now!

We have never said that the PTO should repeat the previous mistakes for which it was highly criticized (like the one click Internet checkout, or the Internet coupons (while it was known that the web was capable of displaying /printing graphical information). We are only asking a fair evaluation and that we would not be required to endure undue process and more burden than the big pharma or other applicants. That includes the issue of obviousness rejection but we have extensively (and I think successfully) shown that others and the cited prior art was not in possession of our invention.

[The enclosed copy from Business2 (page 64 March 2006) is another example of how the obviousness standards were applied in other cases. Another example – as I recall it – is from the Mayo Clinic combining the heating blanket with an operating table and getting a patent for a long felt unsolved need. We are only asking for a fair evaluation so that we would not have to face impossible standards that are also against the purpose of the PTO's mission.]

- 2nd reply **#21);** The examiner's new ground of rejection that was made final in page 13 also involves new ground of rejection **for the dependent claims of Claim 1 and 2** even if not explicitly stressed by the examiner. The same low dose concept was also described for the dependent claims from claims 1-2 prior to the 1st office action (e.g. original claim 9). The examiner introduced new ground for his rejection that was neither necessitated by the applicant's amendment of his claims (as explained below) nor based on information filed in an information disclosure during the allotted time period, thus the final rejection is improper (C.F.R., Title 37, Sec. 1.97 (c).). Although the examiner only mentions infiniteness of low dose for claim 3 (that indeed was amended) the low dose concept equally stands for other claims that depend from claim 1 and 2, (and in original claim 9,). In addition, we submit that the low dose was described in the specification.

The line by line reply to the 2nd (final) office action

(We would follow the same formatting as in the line by line reply to the 1st office action).
For better organization, we put our brief reply in a tables. Indented to the left or left column is the copy of the 2nd office action's pertinent part, indented to right or right column is reference or our brief reply to the 2nd office (action incorporating/referring to the above replies).

ApplicationlControl Number: 101627,358
Art Unit: 1623

Page 2

Detailed Action

This office action is a response to applicant's amendment submitted January 22, 2007 wherein claims 1-3, 6, 14, 15, 41 -43, 48, 49, and 51 -54 are amended, claims 39, 40, and 44-47 are cancelled, and new claims 55-105 are introduced. This application claims priority to provisional application 60131 9436, filed July 30, 2002.

Claims 1-38, 41-43, and 48-105 are pending in this application.

Claims 1-38, 41 -43, and 48-1 05 as amended are examined on the merits herein.

Applicant's amendment, submitted January 22, 2007, with respect to the rejection of instant claim 6 under 35 USC 11 2, second paragraph, for being indefinite for reciting the names, ORG 5222 and SM-9018, has been fully considered and found to be persuasive to remove the rejection as the claims as amended no longer recite said limitations. Therefore the rejection is withdrawn.

Applicant's amendment, submitted January 22, 2007, with respect to the rejection of instant claims 42, 48, 53, and 54 under 35 USC 112, first paragraph, for reciting the term, "preventing," has been fully considered and found to be persuasive to remove the rejection as the claims as amended no longer recite this term. Therefore the rejection is withdrawn.

Applicant's amendment, submitted January 22, 2007, with respect to the rejection of instant claims 1-2, 4-6, 9, 11, 13, 14, 16, 18, 20-22, 24-26, 28-30, 32-35, 37-

Page 3

38,42, 48,49, 51, 53, and 54 under 35 USC 102(b), for being anticipated by Tollefson has been fully considered and found to be persuasive to remove the rejection as the claims as amended recite the further limitation, "at a time selected from the group consisting of, as an initial treatment, as soon as possible, and upon presentation of said patient to a physician or other health care provider." These limitations are not spelled out explicitly by Tollefson. Therefore the rejection is withdrawn.

Applicant's amendment, submitted January 22, 2007, with respect to the rejection of instant claims 1-2,4-6, 9-1 1, 13, 14, 37-38, 42, 48, 51, 53, and 54 under 35 USC 102(e), for being anticipated by Faour has been fully considered and found to be persuasive to remove the rejection as the claims as amended recite the further limitation, "at a time selected from the group consisting of, as an initial treatment, as soon as possible, and upon presentation of said patient to a physician or other health care provider." These limitations are not spelled out explicitly by Faour et al. Therefore the rejection is withdrawn.

Applicant's amendment, submitted January 22, 2007, with respect to the rejection of instant claims 3-6, 9,49, 50, and 51 under 35 USC 102(b), for being anticipated by George et al. has been fully considered and found to be persuasive to remove the rejection as the claims as amended require that the patient be nonpsychotic. Therefore the rejection is withdrawn.

Page **4**

Applicant's amendment, submitted January 22, 2007, with respect to the rejection of instant claims 1-2, 4, 7, 9, 11 -1 5, 37, 38, 42,48, and 51-54 under 35 USC 102(e), for being anticipated by Chappell et al. has beer1 fully considered and found to be persuasive to remove the rejection as the claims as amended recite the further limitation, "at a time selected from the group consisting of, as an initial treatment, as soon as possible, and upon presentation of said patient to a physician or other health care provider." These limitations are not spelled out explicitly by Chappell et al. Therefore the rejection is withdrawn.

Reply A: The PTO is acknowledging that the applicant's arguments were "found to be persuasive to remove the rejection as the claims as amended recite new limitation(s)" and the PTO is withdrawing it's rejections – for all of our claims and arguments.

Then the PTO examiners ignore our arguments and repeats their unconvincing line of resoning in multiple and almost uncountable times – as we have shown that with the above numbered examples.

The PTO (as above) and above Reply-1) to the 1st office action has addressed **Claim 6**: "Claim 6 is rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention". "Claim 6 recites a list of antipsychotic drugs, including, **ORG 5222 and SM-9018**. These names do not clearly and distinctly indicate a particular chemical compound".

However, it should be noted that although we complied with he PTO's request and also made our argument of why the PTO erred with that statement, no comments were made in that regards by the PTO. It is further notable that **WO 02/053140 A2 (page 18 claim 5) application by Pharmacia & Upjohn Company (drug company)** also lists compounds by such names.
Abilify was also known by other names as we have pointed out in our provisional application. (e.g. claim 16 in provisional: aripiprazole {also known as OPC-14597 or Abilitat}. So the PTO erred on that issue too and to our argument on describing the facts the PTO did not make any further comments. If naming the chemical compounds is allowed by big pharmaceutical companies (and research publications were based on these compounds using those names), it than should be allowed the same for a small entity inventor.

Page 4 second paragraph:
An examination of this application reveals that applicant is unfamiliar with patent prosecution procedure. While an inventor may prosecute the application, lack of skill in this field usually acts as a liability in affording the maximum protection for the invention disclosed. Applicant is advised to secure the services of a registered patent attorney or agent to prosecute the application, since the value of a patent is largely dependent upon skilled preparation and prosecution. The Office cannot aid in selecting an attorney or agent.

A listing of registered patent attorneys and agents is available on the USPTO Internet web site http://www.uspto.gov in the Site Index under "Attorney and Agent

Roster." Applicant may also obtain a list of registered patent attorneys and agents located in their area by writing to the Mail Stop OED, Director of the U. S. Patent and Trademark Office, PO Box 1450, Alexandria, VA 22313 -1 450

Reply B: The PTO is acknowledging that the applicant is in need of help. **Yet... see #14-15 and #16**

Page **5**

Claim Objections

Applicant is advised that should claim 1 or 2 be found allowable, claims 59, 60-62, 98-1 03, and 109-1 18 will be objected to under 37 CFR 1.75 as being a substantial duplicate thereof. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Said claims introduce no new limitations to claims 1 and 2 besides stating **various motivations** for the treatment such as, "for resisting suicide," or, "for the benefit of the group of patients." These so-called limitations **do not introduce any new steps** into the method of the original claims, alter any existing steps, or materially alter the patient population. Therefore they are seen to be identical to claims 1 and 2, and thus to be substantial duplicates thereof.

Reply C: The above is incorrect. The PTO errs on not recognizing the additional clinical and inventive steps involved (as described above in #1-5, #8-9,) (risk benefit/alternative analysis, and also the benefit of the group... is just as much of a step than diagnosis on which invention is based.)

'The PTO on page 17 lines 15-17 has specifically acknowledged that "diagnosis and determination of the best course of treatment" consists of steps! Therefore the PTO examiners contradict with themselves when they deny our claims based on calling these steps as "various motivations".'
These steps very much introduce new limitations! Without these steps you could not give the combination therapy as initial treatment and/or for "substantially all" **of said** patients (within the non-TRD and non-psychotic depression as in claims 1,2 that these claims depend on)

I'm glad that we were so explicit with our argument in the provisional application, and that we requested the pertinent parts to be included in the specification under Guidance 2a). (The PTO ignored this request and the content).

> Page 5 of 1st reply: "(One could speculate that if using the SSRI-atypical neuroleptic combination would increase the response rate of treatment-resistant depression, then the percentage rate for improvement would be also higher if given for everybody who is clinically depressed, that is without separating the 'responders' from the 'non-responders'.
>
> This speculation is probably correct, but by itself would not substantiate the added risk using the neuroleptics. With this rationale, the two step strategy would seem still to be the logical step, to treat the depressed patients with antidepressants first, and reserve other strategies for the treatment-resistant group only. In the argument to consider, or start using the combination treatment right away in all those who are clinically depressed, it is the decrease of suicide rate that is the paramount important factor. ..."

Therefore "resisting suicide," or, "for the benefit of the group of patients" are crucial inventive and clinical steps. The secondary factors also testify to that effect.
If resisting suicide would be only a mere motivation, than prenatal vitamins to resist ("prevent") cleft plate or aspirin to resist heart attack would also fall to this category and so would giving an antipsychotic for resisting the emergence of hallucination.

The PTO's such statement (of aforementioned claims being substantial duplicate, or disregarding these steps that the PTO also acknowledged of being steps, but here calling mere "various motivations") is unacceptable not only clinically but also by the patent law principles!

See also discussion under #8, #9, and Figure 3.

As regards to claims 109-118 (as discussed at the phone interview – that was after the 2nd OA – these claims are not duplicate sets of prior claims as they do not have the initial treatment limitation.

From page 5

The following rejection, of record in the previous office action, is maintained:

Claim Rejections - 35 USC 5 112

The following is a quotation of the first paragraph of 35 U.S.C. 11 2:
The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 1-1 5, 36-38,41-43, 48-74, 95-1 06, and 1 09-1 18 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being **enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal** comprising administering certain antidepressants defined in the specification

Page ***6***

and prior art in combination with certain specific *atypical antipsychotic drugs known to be useful for improving therapeutic outcomes in depression*, does not reasonably provide **enablement for such a method involving any antidepressant and any antipsychotic**. The specification **does not enable** any person skilled in the art to which it pertains, or with which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to In re Wands, 8 USPQ2d 1400 (CAFCI988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is a method of treating depression and other disorders by administering a combination of two drugs. It is claimed that the antipsychotic drug improves the therapeutic outcorne even in patients not suffering from psychotic symptoms.

The state of the prior art: *Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art.* The antipsychotic drugs known to be useful in this method are of the newer, atypical variety. **No general theory** has been provided which would explain the usefulness of atypical antipsychotic drugs for treating

Page **7**

depression, or determining which specific drugs are the most likely to be useful. Although a *number of drug combinations have been tested and found to be useful*, particularly combinations of a serotonin reuptake inhibitor with an atypical antipsychotic, many drugs of both types have not been tested. In particular, typical antipsychotics and dopamine system stabilizers such as aripiprazole have not been tested in the claimed methods.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: In the **absence of any general theory explaining the action of atypical antipsychotic drugs to enhance therapeutic outcomes with antidepressants**, it is not possible to predict the efficacy of any particular antipsychotic for this purpose absent experimental data. Because the terms antidepressant and antipsychotic both encompass a large number of drugs of varying structures and methods of action, and because antipsychotic drugs differ significantly from each other as disclosed in Applicant's specification, (p. 13, lines 11-1 5) no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics **generally**. Thus the effectiveness of a particular combination therapy of an antidepressant and an antipsychotic for the treatment of depression, cognitive distortions, smoking cessation, or nicotine withdrawal is **unpredictable**.

The Breadth of the claims: The claimed invention encompasses combination therapies of **any antidepressant with any antipsychotic**. In particular, it encompasses combinations in which the antipsychotic is a typical or an atypical antipsychotic, or a

Page **8**

dopamine system stabilizer. *While some of the aforementioned claims recite specific antidepressants or specific antipsychotic agents, they are all generic to at least one component of the combination.*

The amount of direction or guidance presented: *Two hypothetical cases* are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-1 7)

The presence or absence of working examples: *No working examples* of the claimed therapeutic methods is provided by Applicant.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an **unpredictable and undeveloped art** such as antidepressant/antipsychotic combination therapy. See MPEP 21 64.

The quantity of experimentation necessary: **In order to practice** the claimed invention, one skilled in the art would be required to determine the extent of antidepressants and antipsychotics useful in said methods. Because Applicant has provided no working examples, and because the state of the art is unpredictable, many different combinations would need to be tested **in order to provide a comprehensive understanding of which combinations are or are not useful in the claimed method**. These experiments would be repeated for each combination in **animal models** of depression, cognitive distortions, and nicotine addiction, in order to establish their suitability as therapeutic methods. It should be noted that evaluating psychological disorders such as depression and cognitive distortions in animals is more difficult than evaluating a therapy for a nonpsychological condition such as cancer or arthritis. Animal experiments include, along with the actual administration of the potential

Page **9**

pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Because of the unpredictability of the art

and the lack of any generalized method for predicting the pharmacological properties of any arbitrarily chosen molecule, these animal experiments would need to be repeated many times, and involve the maintenance, **killing**, and disposal of many experimental **animals**, to establish the suitability or lack thereof for each compound found to possess the desired activity in vitro.

The scale of animal testing described in the preceding paragraphs would present an undue amount of unpredictable experimentation to require of anyone wishing to practice the invention.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the unpredictability of the art and the lack of guidance or working examples, Applicants fail to provide information sufficient to practice the claimed invention with **every possible antidepressant and antipsychotic.**

Reply D: The PTO acknowledges that our method is **enabling for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal.**

However, the PTO argues that these claims are not enabling for **involving any antidepressant and any antipsychotic.** That brings up the questions that we discussed under #6 (moved to above #17), and #16-19 and particularly under #17. We have shown the inconsistency and the PTO error. Never the less **we amended claims** 1-3 and 109-118 as suggested by the PTO.

The statement of *"atypical antipsychotic drugs known to be useful for improving therapeutic outcomes in depression"* can be misleading and was discussed in **Reply-2 of the 1st OA.**

The misleading issue of *"Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art."* And later again: *"number of drug combinations have been tested and found to be useful"* were also addressed in the **reply to the 1st OA.**

"No general theory And again: **absence of any general theory explaining the action of atypical antipsychotic drugs to enhance therapeutic outcomes with antidepressants**, it is not possible to predict the efficacy" is simply an incorrect statement by the PTO as it was again discussed **under #16.**

"Because the terms antidepressant and antipsychotic both encompass a large number of drugs of varying structures and methods of action, and because antipsychotic drugs differ significantly from each other as disclosed in Applicant's specification, (p. 13, lines 11-1 5) no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics **generally**. Thus the effectiveness of a particular combination therapy of an antidepressant and an antipsychotic for the treatment of depression, cognitive distortions, smoking cessation, or nicotine withdrawal is **unpredictable**." is **a misquote by the PTO** as discussed under #17, and #6, and #16.

any antidepressant with any antipsychotic is the same issue as the second paragraph here in this box and was discussed under #6, and #16-19.

While some of the aforementioned claims recite specific antidepressants or specific antipsychotic agents, ***they are all generic*** *to at least one component of the combination.* It is not clear to the **applicant of what that means and what the problem is with this.** Claim 5 for example recites some currently used antipsychotics wherein claim 14 recites some antidepressants. The prior claims that these claims depend on describe of how to use the combination. However, #6, #16,-19 further elaborated on enablement if that is the problem. Amended claim 10 describes specific antidepressants and antiposychotics (and the same is true for claims 16-35, 75-94.)

In regards to **"unpredictable and undeveloped art"** first of all it needs to be put in a context. The PTO acknowledged already consequent to the PTO's statement at page 10 that this is not so for the currently known drugs in psychiatry. [The same is true for PTO page 12, see Reply I(i)]. The second paragraph here and our discussion under #6, and #16-19 shows that the art for the aforementioned classes of medications is predictable, developed and in fact crowded. We have enabled the artisan for these classes of medications.

Consequently the following are all incorrect: "In order to practice the claimed invention, one skilled in the art would be required to determine the extent of antidepressants and antipsychotics useful in said methods....

...because the state of the art is unpredictable, many different combinations would need to be tested **in order to provide a comprehensive understanding of which combinations are or are not useful in the claimed method**. ...
These experiments would be repeated for each combination in **animal models ...**
...killing of **animals**, ...

...every possible antidepressant and antipsychotic.
These PTO statements were addressed above and in the numbered (#-d) paragraphs.

Page 9:
Response to Argument: Applicant's argument, submitted January 22, 2007, with respect to the above rejection has been fully considered and **not found to be persuasive**

Page **10**

to remove the rejection. Applicant argues that the claimed invention falls within the common and routine practice of off-label administration of FDA-approved drugs to different patient populations from those for which they were originally approved, and which has already been practiced with the claimed drugs for different indications. This argument is persuasive only for those antidepressants and antipsychotics which are in fact in common use for other indications and can reasonably be prescribed off-label. The claims as written use **functional language** which is not limited only to drugs **currently known, such as serotonin reuptake inhibitors, dopamine system stabilizers, and the like**. Rattler, the claims as written include methods of treatment using any compound whatsoever that happens to have any antidepressant or antipsychotic activity. In all likelihood, many such compounds are not yet known, much less prescribed and available for off-label use.

Reply E: The PTO acknowledges that our argument "is persuasive ... for those antidepressants and antipsychotics which are in fact in common use for other indications and can reasonably be prescribed off-label."

The issue of the "functional language which is not limited only to drugs

currently known, such as serotonin reuptake inhibitors, dopamine system stabilizers, and the like...
...any antidepressant or antipsychotic activity. In all likelihood, many such compounds are not yet known,.." were discussed above and under Reply D; #6, and #16-19, and extends our "persuasive" argument to the classes of medications, therefore to substantially all the claims, especially as we have amended those claims adhering to the PTO's suggestion.

Page 10:
Applicant's statements with regard to the **theory** behind the claimed invention have been considered, but are **not relevant to** the issue of **functional language** raised above. The problem for a skilled practitioner in the art, as described in the previous paragraph, is that drug species have been claimed by the functional language of instant clams 1-3 that are not currently known to have any psychiatric utility. A skilled practitioner cannot reasonably be expected to prescribe off-label a compound which he does not know to have a therapeutic effect, and whose psychiatric effects and interactions with other drugs have never been observed in any human or animal subject for any indication.

Reply F: **"theory** ... **not relevant to** the issue of **functional language"** is an incorrect statement by the PTO as the theory involved the general class of medications. See also #16-17, & #6.

Page **11**
Applicant's argument with respect **to Einstein's theory of relativity is not relevant** to the instant case because Einstein developed no practical application for the theory of relativity. Facts of nature (which are always unpatentable) are harder to clearly and definitively prove than inventions having a specific, practical utility. If Einstein had invented a process, machine, manufacture, or composition of matter based on the theory of relativity possessing a real-world utility, the enablement of said invention would likely have been proven well before the theory of relativity itself had been proven and would not have required atomic clocks to test. Therefore Applicant's invention cannot be compared to a scientific theory.

Reply G: The PTO is derailing from the point we have made. The point is that **a patent needs enablement and if that is provided no experiment is needed.** The PTO already acknowledged exactly the same point above Reply E and H in talking about the off label use medications.

Einstein's theory of relativity was brought up in "as if" scenario and is relevant in showing that sometimes breakthrough approaches cannot yet be proved by experiments.
We have also argued that the expenses are out of the limit of this small entity inventor. Similar examples could be brought up for inventions on a new space shuttle to Mars or to a different galaxy. While nobody would have the time – in patent terms – to wait for an experiment to reach another galaxy, and provide the experimental "proofs" for the patent office, a small entity inventor or even many nations would not have the assets to experimentally prove and finance such a mission. The enablement would not have to be based on experiments, but on whether or not the inventor provided logical steps not recognized by others, and whether or not the inventor had given adequate guidance to enable the skilled in the art to practice the invention without expensive experimental data! (That was the relevant point that we were making).

That also means – for the interest of the applicant to ensure the likelihood of patentability – that the inventor would be expected to go an extra mile with the guidance provided, as much as it is possible. As we have shown we had done that and went beyond in our provisional application even surpassing the expectation of the PTO examiner and even gave a synthesis for depression of how the aforementioned medications, the biological, psychological and [genetic – gene expression] – changes interact with each other.

We could come to the same conclusions also if you look the history of the PTO: – as my formerly representing attorney (Mr Arni Silverman) have told me – his client (whose identity he did not disclose) was granted a patent the very first time in the PTO's history without any human experiment on an anticancer drug due to their surprising result and because the need for that drug.
That shows our point – and **what the PTO acknowledged already** for drugs used off label – that the enabling and the inventive steps are the crucial factors, and not the experiments. (See Reply H)

Page 11:

Applicant also notes that the **cost of a study** of the clinical efficacy of a drug is **prohibitive** and **that such studies are not required for off-label use.** As stated earlier, Applicant's functional language encompasses not only those drugs currently on the market and available for off-label use, but also those which have not yet been discovered. ***Even the simplest in vitro and in vivo experiments*** needed to discover new classes of antidepressants and antipsychotics (referring to high-throughput screens used in the earliest stages of drug discovery, and not to $40 million government-funded clinical studies***) would, when repeated for every compound under the sun, involve a burden of experimentation,*** including ***synthesis and screening of millions of compounds*** at least and follow-up experiments on all promising leads, that would constitute ***undue and unpredictable experimentation.*** Applicant should note that none of this experimentation is necessary for the off-label use of currently known drugs (e.g.

Page 12

fluoxetine or ziprasidone). ***but only for drugs not currently known in the art for any psychiatric use.***

Reply H: . The PTO is acknowledging that **a patent needs enablement and if that is provided no experiment is needed by saying "that such studies are not required for off-label use."**

This was also our reason of bringing up the prohibitive costs for some of these experiments. Our theory (#16) and guidance specifically enables the clinician to use the invention for the aforementioned class of drugs thus enabling substantially all the claims (specifically as we have **amended** them).

Otherwise the same applies as discussed under **Reply D-G.**

Page 12

Applicant further argues that the relevant art is predictable, and in fact crowded, as evidenced by the many drugs on the market and their routine off-label use. While **this statement is true** as regards those classes of **drugs already known to be psychiatric drugs**, *Applicant's open-ended claim language reaches far beyond the known and predictable art*. Such open-ended language greatly reduces the predictability of an invention.

For these reasons, the rejection is upheld and made FINAL. With regards to new claims 55-1 18, the rejection of these claims was necessitated by Applicant's amendment and is thus properly made final.

Reply I (=i): goes back to Reply D-H,
PTO acknowledged that the art is predictable, and in fact crowded for known drugs. The argument with analogy of SSRI and other pharmaceutical company patent, is resolving this conflict. (Reply D-H).

Page 12

Applicant's amendment, submitted January 22, 2007, necessitates the following new grounds of rejection:

Claim Rejections - 35 USC 5 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:
The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claims 3-38, 49-52, 54, 56, 58, 61-94, and 97-1 07 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention. The base claims 3, 56, and 58 state that the antipsychotic drug is administered at a low dose. **No**

Page **13**

indication is given as to what a low dose is or what it is low relative to. No guidance is given in the claims or the specification to allow one skilled in the art to know, for example, how low the dose can be and still retain activity, or how high it can be and still be considered low. Therefore claim 3 and its dependant claims are indefinite. Because Applicant's amendment necessitated the new ground of rejection above, the rejection is made **FINAL.**

Reply J: It is for the record that this concern was not brought up (this way) by the examiner in the 1st office action. (e.g. original claim 9). However in our reply to the 1st OA we were specific of why the low dose makes a difference over the prior art documents. The PTO misinterpreted or ignored our arguments.

The PTO errs with all of these statements. Both the provisional and the utility application specifically described the meaning of the low dose.

Page 9 lines 10-25 of the utility: "In the method of the present invention, the dosage of the antipsychotic drug should **be around approximately one-third (1/3) to the average dose** of the amount normally prescribed. However, a lower than average dose is preferred for most cases. At times minimal dose can be expected to be sufficient, like for quetiapine 25-50mg, (if needed raised up to 300-400 mg q.d.), for risperidone 0.5-1mg (if needed raised to 2-4 mg q.d.), for olanzapine 2.5 mg-5mg, (and at times used at 10 mg q.d.), or for ziprasidone 10-20mg (at times at 40mg), and most likely, for aripiprazole 2.5-10 mg q.d. or less; (if needed given at 15mg q.d.) as an example.

It should also be understood that these doses are not fixed, and a lower dose may be effective for some, but not for others. In the case of the atypical antipsychotics and dopamine system stabilizers, a higher dose (similar to the doses given for psychosis) may be effective in the prevention of suicide. The exceptions from this are the doses when EPS and other side effects occur. However, it is best to expose the patient to the least amount of effective medication. In addition lower doses may have other benefits as well."

It is notable as we have discussed in our reply to the 1st office action, that the PDR gives target dose for the antipsychotics (and we have also discussed that the target doses in the literature is described often as higher than the PDR doses. These should be known to the

artisans).

Page 14 lines 28-31, page 15 lines 1-2: "If typical (or conventional) antipsychotics are used as adjunct to antidepressants a low dose should be given. The doses of the typical antipsychotics are also often given in "chlorpromazine equivalent" doses. (See e.g. conversion charts at DeBattista, C. et al 2003, p91; Jenkins S.C. et al 1990, p134). A low dose of an antipsychotic would mean a chlorpromazine equivalent" dose of 25-50mg, or up to 100-150mg q d."

The hypothetical examples also supported the low dose concept. (See also Reply Q (q), R).

Our theory and reasons on to using the atypical antipsychotic medications for the purposes provided are further enabling for the artisan. That is also true about the interaction of the medications with the psychological aspects of depression and the indirect but targeted effect of medications on the treatment of depression.

Moreover we have specifically disclosed Page 2 line 6-8 of utility that: "antipsychotic drugs, including some of the atypical antipsychotics, may even have depressogenic properties."
That is further enablement to the artisan as we had detailed reasoning in the 1st reply (that the PTO ignored). The same stands for "10 d)" on treatment emergent akathisia linked to treatment emergent suicidality at high doses, that we have discussed in regards of Faour reference at here at pages 12-13. That also included reference on page 4 line 19 in our utility application.

So the PTO's (new) statement of the **"No indication is given as to what a low dose is"** or that **"No guidance is given"** in that regard to the clinician and "**therefore** claim 3 and its dependant claims are indefinite" **is bona fide incorrect and erroneous statement by the PTO**.
There are variations in the clinical art, but we have defined the low dose so that the average artisan could without undue experiment apply our guidance. We have also discussed our enabling in this regard in particular with comparison to the cited prior art in our reply to the 1st office action. The PTO makes erroneous conclusions based on erroneous statements!

Furthermore as mentioned under 2nd reply #21, the PTO gave only a rejection of the low dose concept for claim 3 and not for the dependent claims from claims 1 and 2. (or the original claim 9,).

See also Reply R as continuation of this reply with further and essential information.

Page 13

Claims 55, 57, 60, and 63-1 08 recite the limitation "treating substantially all patients treated by said physician". There is insufficient antecedent basis for this limitation in the base claims 1 and 2. Said base claims include the negative limitation that the patient's depression not be psychotic or treatment-resistant. Therefore according to the base claims, the practitioner does not treat patients displaying psychosis or treatment resistance by this method. There is therefore insufficient antecedent basis in the parent claims for the new limitations introduced in claims 55 and 57.

Because Applicant's amendment necessitated the new ground of rejection above, the rejection is made **FINAL.**

The following is a quotation of the first paragraph of 35 U.S.C. 112:

The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Reply K: This is a misinterpretation by the PTO as discussed under #9, and would be resolved by amending the claims.

It should be clear that we did not mean to introduce new limitations based upon the content of our amendment and the language of the neighboring claims. We specifically asked the PTO to allow amendment of our specifications from the provisional application (Guidance 2a) from the reply to the 1st office action. Claims 55, 57 would be amended as "treating substantially all **of said** patients".

Page **14**

Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted January 8, 2007 with respect to claim 65 has been fully considered and but is deemed to insert **new mater** into the claims since the specification as originally filed does not provide support for the active metabolite of risperidone. As the instant specification as filed contains no description of said metabolite or a method of using it as a therapeutic agent, the specification as originally filed does not provide support for the subject matter of instant claim 65. See in re *Smith,* 458 F.2d 1389, 1395,173 USPQ 679,683 (CCPA 1972).

Because Applicant's amendment necessitated the new ground of rejection above, the rejection is made **FINAL.**

Reply L: This was described under #10 above.

Page 14

Claims 55, 57, 60, and 63-108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

Applicant's amendment submitted January 8, 2007 with respect to claims 55, 57, 60, and 63-108 has been fully considered and but is deemed to insert **new mater** into

Page **15**

the claims since the specification as originally filed does not provide support for a therapeutic method in which an antidepressant and an antipsychotic drug are administered to all patients treated by a physician or health care provider regardless of diagnosis or other considerations. The specification as filed (pp. 5-7, Summary of the Invention) only describes methods for treating patients having non-psychotic, non-treatment resistant depression, which is a specific clinical indication not shared by everyone who presents themselves to a health care provider, or other similarly specific conditions. See in re Smith, 458 F.2d 1389, 1395, 173 USPQ 679,683 (CCPA 1972).

Because Applicant's amendment necessitated the new ground of rejection above, the rejection is made **FINAL.**

Reply M: This is a misinterpretation by the PTO, and would be resolved by amending the claims as "substantially all of said patients".
This was described under #9 above. Same applies as under **Reply K.**

Page 15

Claims 55, 57, 60, and 63-1 08 are rejected under 35 U.S.C. 1 12, first paragraph, as failing to comply with the enablement requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention.

The Applicant's attention is drawn to In re Wands, 8 USPQ2d 1400 (CAFCI 988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1 986) at 547 the court recited eight factors:
(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims;

Page **16**

(6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed method is a therapeutic method. Therapeutic methods, in order to meet the enablement requirement, must be disclosed in such a way that a skilled practitioner could reasonably be expected to practice said invention within the general guidelines of the art.

The state of the prior art: The medical art is a matter of life and death importance. In particular, it involves the administration of many drugs having severe and even potentially life-threatening side effects. As indicated by Applicant in his arguments submitted January 22,2007, **antipsychotic drugs possess such severe and potentially life-threatening side effects**. Furthermore, **antipsychotic drugs are only known to be of benefit from patients having a psychiatric disorder involving psychosis or psychotic-like symptoms.** (such as disordered thinking, delusions, or hal4ucinations) **Subjects not having these conditions will experience the side effects of the drugs without any benefit. Thus these drugs must not be prescribed** without careful consideration of a patient's situation and **whether the patient will benefit from them**. A skilled practitioner would not, for example, sell antipsychotic drugs in a vending machine in the lobby of his office.

The usual practice in the art is to diagnose a patient with a particular disorder or symptom **before deciding on a course of therapy, and to administer therapy only to patients reasonably believed to benefit from said therapy. The benefits of this approach include the avoidance of unnecessary side effects** and the improved efficacy of therapy

Page **17**

resulting from administering to a patient a drug which is not suited to his condition. In addi.tion to the issues mentioned above, automatic distribution of drugs to every patient carries a strong risk of enabling abuse of those drugs.

While it is a cliché that psychiatric disorders are merely extreme versions of common personality traits and that therefore, "everyone is a little bit crazy," it does not therefore follow that the average person would benefit from antipsychotic drugs. Even if this were the case, many patients would likely refuse therapy because they do not suffer appreciably as a result of their non-pathological personality quirks and do not particularly wish to take drugs, particularly drugs with serious side effects, in order to alter their personality.

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: All sorts of people seek medical attention. A skilled practitioner cannot assume that every patient who walks into his

office suffers from non-psychotic, non-treatment-resistant depression, or that all patients would benefit from antipsychotic drugs. Much of the job of a skilled practitioner involves **diagnosis and determination of the best course of treatment for a patient. Once these steps** have been removed form the decision of what therapy to pursue, the outcome of treatment is by definition highly unpredictable.

The Breadth of the claims: The instant claims are drawn to a method of administering a combination of an antidepressant and an antipsychotic drug to everyone who seeks treatment from the practitioner. This includes patients having a condition treatable by said drugs, patients having no condition treatable by said drugs, and

Page **18**

patients who are trying to obtain the drugs for purposes such as abuse or resale. Essentially, said claims involve treating antidepressants and antipsychotic drugs as unregulated, nonprescription drugs comparable to aspirin.

The amount of direction or guidance presented: Applicant's specification provides no evidence that antidepressants and antipsychotic drugs can be safely distributed to the general population without the carefully controlled regime of diagnosis and prescription that is currently in place for these drugs.

The presence or absence of working examples: Two hypothetical examples are provided. In both cases the patient is examined and diagnosed with non-psychotic depression. In neither case is medication administered in the absence of a diagnosis. In both cases medication is discontinued after a certain period of time, rather than being always administered for all patients.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the administration of drugs without diagnosis. See MPEP 2164.

The quantity of experimentation necessary: In order to practice the claimed invention, one skilled in the art would need to be in possession of antidepressants and antipsychotics lacking in side effects and suitable for administration to the general population of subjects presenting themselves to a physician, including patients not actually diagnosed with any psychiatric disorder. Up to now, the search for new psychiatric drugs has failed to uncover any which are safe to use outside of a careful diagnosis and prescription. As these drugs act on a very complex and central biological

Page **19**

system (i.e. the brain) there is no reasonable expectation that such drugs exist. If they do, discovering them would involve an intensive research program of screening millions of compounds against multiple targets involved in depression and psychosis and then testing the hits obtained from these screens fore side effects. The claimed invention therefore requires undue and unpredictable experimentation to practice.

Genentech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but **compensation for its successful conclusion**." And "patent protection is granted **in return for an enabling disclosure** of an invention, **not for vague intimations of general ideas that may or may not be workable**."

Therefore, in view of the Wands factors, as discussed above, particularly the state of the prior art and the **lack of guidance presented**, Applicants fail to provide information sufficient to practice the claimed invention for the treatment of all patients.

Because Applicant's amendment necessitated the new ground of rejection above, the rejection is made **FINAL.**

Reply N: This is a misinterpretation by the PTO.
This was described under #9 above. Same applies as under **Reply K and M.**

However, it is of note that the PTO's quotation bolded from page 16, was used **for #1** reply here (page 17), in pointing out contradictions between PTO statements.

The bolded parts from page 17 above was used **for #8** reply here, in pointing out that the PTO acknowledged that the "determination of ... treatment" consists of steps! Therefore the **PTO examiners contradict with themselves** when they **deny our claims** based on calling these steps as "various motivations". (#8).

The ***Genentech* factors** (with our secondary factors) show that we made a successful conclusion that the others in the art failed to do, and that we have enabled the artisan, thus we are entitled to a patent.

However, the same ***Genentech* factors** should be applied by the PTO against the cited prior art and as we have shown none of the cited prior art gave the conclusions or enablement that we have provided, (and we have provided our guidance in great details).

The PTO's statement on the "lack of guidance presented" is due to the PTO misrepresenting our intended language.

Page 19

Claims 43, 98, 109, 110 rejected under 35 U.S.C. 112, first paragraph, because the specification, while being **enabling for a method of treating depression and associated conditions, and avoiding, protecting against, or remedying relapse or recurrence of depression,** does not reasonably provide enablement for preventing depression or the progression or relapse thereof, or preventing suicide. The specification does not enable any person skilled in the art to which it pertains, or with

Page 20

which it is most nearly connected, to practice the invention commensurate in scope with these claims.

The Applicant's attention is drawn to In re Wands, 8 USPQ2d 1400 (CAFC1988) at 1404 where the court set forth eight factors to consider when assessing if a disclosure would have required undue experimentation. Citing Ex parte Forman, 230 USPQ 546 (BdApls 1986) at 547 the court recited eight factors:

(1) The nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

Nature of the invention: The claimed invention is drawn to a method of preventing suicide, relapse of depression, or various complications thereof, by administering to a patient in need thereof a combination of an antidepressant and an antipsychotic.

The state of the prior art: Combination therapy with antidepressants and atypical antipsychotic drugs has been taught in the prior art for conditions such as psychotic depression or bipolar disorder. The antipsychotic drugs known to be useful in this method are of the newer, atypical variety. The prior art does not teach a method of **preventing** recurrence or relapse of depression through antidepressant/antipsychotic combination therapy, or of **preventing** suicide. As evidenced by the existence of treatment-resistant cases of depression, no therapy is **100% effective at preventing** the progression, recurrence, or relapse of depression.

Page **21**

The relative skill of those in the art: The relative skill of those in the art is high.

The predictability or unpredictability of the art: Because the terms antidepressant and antipsychotic both encompass a large number of drugs of varying structures and

methods of action, and because antipsychotic drugs differ significantly from each other as disclosed in Applicant's specification, (p. 13, lines 11 -1 5) *no one example of group of related examples can be predictive for demonstrating the effectiveness of antidepressants combined with antipsychotics generally*.

Furthermore, depression denotes an observed symptom rather than an underlying condition. Different cases of depression differ from one another to the extent that a skilled practitioner must determine the best course of therapy empirically by administering one drug after another to a patient in order to find one which elicits a positive response. Thus it is highly unlikely that it is possible in all cases of depression to **prevent** progression, recurrence, or relapse with 100% certainty. Thus the prevention of progression, recurrence or relapse of depression is highly unpredictable.

In the case of cognitive distortions, smoking cessation, and nicotine addiction, the art is even more unpredictable. Both cognitive distortions and addictions have a strong psychological component, and the motivation of a patient to change is an essential factor in determining treatment outcome, and one which cannot be improved by any drug therapy. In particular, smoking cessation is rather difficult even with the aid of drug therapy, and most smokers who attempt to quit eventually suffer a relapse and start smoking again. Thus the treatment outcome in the treatment of cognitive distortions and nicotine addiction is highly unpredictable.

Page **22**

Suicide is an action rather than a pathological condition or symptom, and is the result of the interaction of various voluntary, involuntary, and semi-voluntary factors within a patient's condition. Any subject who displays a minimal level of functioning is physically capable of committing suicide, though motivation to do so is usually present only in extreme cases. Short of, for example, incapacitating doses of tranquilizers, no drug therapy can render a patient incapable of killing himself.

While **certain drug therapies can affect the cognitive distortions that predispose a subject to suicide or to relapse in smoking cessation**, these cannot be regarded as a 100% certain guarantee that the subject cannot, no matter what, smoke or commit suicide.

The Breadth of the claims: The claimed invention encompasses combination therapies of any antidepressant with any antipsychotic. In particular, it encompasses combinations in which the antipsychotic is a typical or an atypical antipsychotic, or a dopamine system stabilizer. **Prevention is interpreted to mean the complete, 100% effective elimination of any progression, recurrence, or relapse of the disease while the patient is maintained on the therapy.**

The amount of direction or guidance presented: Two hypothetical cases are given in order to illustrate possible uses of the claimed therapeutic method. (p. 16-1 7) No reason is given to suppose that he claimed methods are perfectly effective at preventing progression, recurrence, or relapse of any instance of major depressive disorder,

Page **22**

The presence or absence of working examples: No working examples of the claimed therapeutic methods is provided by Applicant.

Note that lack of working examples is a critical factor to be considered, especially in a case involving an unpredictable and undeveloped art such as the prevention of disease. See MPEP 2164.

The quantity of experimentation necessary: The **short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness** for prevention of disease. Because no guidance is given for the use of the claimed therapeutic method for the long-term prevention of disease, one skilled in the art wishing to practice the invention would be unable to do so **without first gathering information as to the long-term effectiveness of the therapy**. Furthermore, in order to prevent recurrence of depression, cognitive distortion, or nicotine addiction as described above,

the claimed therapeutic method, which comprises nothing more than administering a drug, must be able to fully counteract the effects of genetics and psychology in order to prevent the subject from ever becoming depressed, having distorted cognition, or smoking again, regardless of the subject's motivation, or any environmental stresses which may encourage the re-emergence of the subject's condition. Such a method would represent a significant novel improvement beyond anything disclosed in the prior art or in Applicant's disclosure, particularly in light of the high relapse rate for smokers attempting to quit.

I In order to develop such a method in the absence of any existing data, one skilled in the art, in order to practice the invention, **would undertake long-term**

Page 24

human or animal tests in order to study the effectiveness of the claimed therapy for preventing recurrence or relapse after the initial recovery. Animal experiments include, along with induction of the disease state, administration of the potential pharmaceutical compound and collection and analysis of data, additional burdens associated with compliance with animal welfare regulations, care, feeding, and other maintenance of the animals, dissection of dead animals to collect data, and disposal of dead animals after the protocol is finished. Human tests impose additional ethical and regulatory burdens.

Performing these studies with no guidance from Applicant or from the prior art is an undue amount of experimentation needed in order to practice the full range of the claimed invention.

Genetech, 108 F.3d at 1366, sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable."

Therefore, in view of the Wands factors, as discussed above, particularly the lack of precedent in the art for prevention of relapse and the *lack of guidance from Applicant's disclosure*, Applicants fail to provide information sufficient to practice the claimed invention ***for the prevention of regression, recurrence, or relapse of disease***.

Reply O: The PTO acknowledges the **enabling for a method of treating depression and associated conditions, and avoiding, protecting against, or remedying relapse or recurrence of depression,** but states that does not reasonably provide enablement for preventing depression or the progression or relapse thereof, or preventing suicide, because the prevention should be 100% and not as used in the medical term of "preventive medicine". That was discussed under # 7, with the **amendment of changing the wording "prevention" to resisting**. The issue of the importance of "resisting depression, or the progression or relapse thereof, or resisting suicide" had been discussed under various parts, like #8-9.

The issue of "*no one example of group of can be predictive generally"* was discussed under #6, #16-19.

Next, the PTO examiner is engaging in a discussion of "**Suicide is an action** rather than a pathological condition or symptom, and is the result of the interaction of various" factors. However the fact for our new way of viewing this issue with our extensive guidance and argument was left out about that suicide is preceded by a thought, specifically a disorder of the thought and that in turn can be targeted with our new method (with our other enabling guidance and reasons)! We have also provided additional steps of risk benefit analysis for our method, which is necessary for enablement. (See also our comparison of suicide rates in the terminally ill along with other convincing arguments in Appendix A of our reply to the 1st OA which was taken from our provisional application, and in our utility). In our

reply to the 1st OA (pages 62 line 32 to page 66 line 2) we specifically argued that the PTO's line of reasoning for obviousness was not convincing, and that cognitive distortions and depression are not the same. We have revisited this here under Reply Q (q), and at the very beginning of our reply to the 2nd OA. (Page 5 of this document).
Next, the PTO examiner states that "no drug therapy can render a patient incapable of killing himself." However, that does not preclude new invention of great importance from patentability to reduce the suicide rate, with using the wording of resisting suicide in the claims. As we have shown the PTO errs of that being only various motivations when it includes steps. (See also #8-9.)

It is notable that "**certain drug therapies can affect the cognitive distortions that predispose a subject to suicide or to relapse in smoking cessation**," on page 22 was not known in prior art, as we have described that at page 5. The mistake for the PTO to assume that, or suggest that assumption is incorrect specifically by excluding the possibility that other methods (like ours) could specifically target the cognitive distortion. We have proven that possibility through our enablement on how antipsychotics (and antidepressants) act. It is important to point out that distinction. No prior art references as to the mechanism of actions of drugs targeting cognitive distortions were given by the PTO. As we have shown the lines of reasoning by the PTO were not convincing for obviousness on prior art. We were the very 1st one not only for bringing up that these classes of medications (both antidepressants and antipsychotics) target cognitive distortions but to give guidance, theory and reasons (thus enablement) for the perceived mechanism of action of both these classes of drugs targeting cognitive distortion. (See also Appendix A and C of our reply to the 1st OA which was taken from our provisional application).

Although the PTO is talking about prevention, and it is the wording change (or definition of the term) that would be deciding on the patentability, it is important to note that the issue of "**short-term usefulness of a therapy for relief of symptoms is no guarantee of its long-term usefulness**" was discussed in the (1st OA) Reply (e.g.: Reply 1, & 20 olanzapine example), and the double standard against the "big pharma" and this small entity applicant was raised. The PTO did not respond to that, but repeats the same double standard demand toward this applicant with the need of extensive and long term animal and human experiments.

Page 24

Response to Argument: Applicant's argument, submitted January 22, 2007, as applied to the above rejection has been fully considered and not found to be persuasive to remove the rejection. Applicant's arguments are all based on the interpretation that the term, "prevention" denotes a treatment that is not necessarily one hundred percent

Page **25**

successful and need not be permanent in its effects. Applicant cites certain examples, such as the approval of prenatal vitamins for the "prevention" of cleft palate and aspirin for the "prevention" of heart attack. This line of argument is not persuasive because the term "prevention" has various meanings in the medical and legal art as well as various meanings to laypeople. For the purposes of patent prosecution, the term "prevention" is used as a legal term specifically referring to the perfect and absolute blocking of any possibility of a disorder in the future. For these purposes, prenatal vitamins do not prevent cleft palate, aspirin does not prevent heart attack, and vaccines do not prevent influenza.

Therefore the rejection is deemed proper and maintained. Because Applicant's

amendment necessitated this rejection, the rejection is made **FINAL.**

Reply P: That was discussed under # 7, and Reply O.

Page 25

Claim Rejections - 35 USC 5 703

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth il-I this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 1-6, 9, 1 1, 13, 14, 16-1 8, 20-22, 24-26, 28-30, 32-37, 41-43,48,49, 51, 53, 54-68, 70, 72, 73, 75-77, 79-81, 83-85, 87-89, 91 -1 04, and 109-1 18 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefson. (PCT international 1
publication W099161027, included by applicant with PTO-1449) Tollefson discloses a method of treating depression by administering both a serotonin reuptake inhibitor and

Page **26**

an atypical antipsychotic. While one embodiment of this invention is a method of treating treatment-resistant depression, another embodiment is a method of providing **rapid onset treatment** of depression to a patient, (p. 2, lines 10-1 3) **which is drawn to cases which have not demonstrated treatment resistance**. Specific atypical antipsychotic drugs which may be administered in this method are olanzapine, clozapine, risperidone, sertindole, quetiapine, and ziprasidone. (p. 3) **Specific serotonin reuptake inhibitors** which may be used are fluoxitene, duloxetine, venlafaxine, milnacipran, citalopram, fluvoxamine, paroxetine, and sertaline, (p. 4, line 5 - p. 5, line 14) Recommended dosages are given on p. 13. *Tollefson does not disclose a method in which the antipsychotic is administered according to the dosage levels disclosed* in instant claims 36 and 95. *Tollefson does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method wherein treatment is giver1 for preventing suicide. Tollefson also does not explicitly disclose a method of treating cognitive distortions* as defined by Applicant's specification on p. 15, lines 9-14.

It would have been obvious to one of ordinary skill in the art to administer the drugs in the methods of Tollefson et al. at the dosages describes in instant claims 36 and 95. It would have been **obvious** to one of ordinary skill in the art at the time of the invention to administer the therapeutic method of Tollefson to a patient **as initial treatment as soon as possible**, and to provide treatment in order **to prevent suicide**, as described in instant claims 39, 41, and 43, **and to treat cognitive distortions** according to

Page **27**

instant claims 3 and 49. One of ordinary skill in the art would have been motivated to practice the therapeutic method in this way because Tollefson discloses that his method is useful **for providing rapid onset treatment, and thus for providing immediate treatment for emergency cases where time is of the essence, such as those in which the subject is at serious risk of suicide**. One of ordinary skill in the art would have been motivated to use the doses described in instant claims 36 and 95 because the ranges disclosed in this claim overlap with those disclosed on p. 13 of Tollefson et ai. One of ordinary skill in the art would have been motivated to use the method for treating

cognitive distortions because cognitive distortions as defined by Applicant are often associated with depression. One of ordinary skill in the art would **reasonably have expected success in using the dosages** of instant claim 36 because these dosages overlap with those taught by Tollefson et al. and **because adjusting dosages within the general range known** in the prior art is **well within the level of ordinary skill in the art**. One of ordinary skill in the art would reasonably have expected success in administering treatment as soon as possible to prevent suicide because suicide is known to correlate strongly with depression, and **because treating a subject for a serious condition as son as possible is a generally recognized practice in the art**. One of ordinary skill in the art would reasonably have expected success in treating cognitive distortions because treating the associated depression would lead to improvement in the associated cognitive distortions.

With respect to the various motivations included in the claim limitations, for example, claims 109-11 8, these limitations describe **various motivations** for

Page **28**

administering the claimed therapeutic agents to a patient suffering from depression or cognitive distortions, **they do not materially alter the actual scope of the claims.** Therefore they do not render the claims non-obvious over the prior art.

Thus the invention taken as a whole is *prima facie* obvious.

Reply Q (q): All these PTO unconvincing line of reasoning are conclusions deviating from the standard of care and the clinicians' thinking as it was discussed previously under #1, #2, Figures 1, and 2; #5, (and in the disregarded parts of the reply to the 1st OA). This issue was also referenced in defending against Faour at the beginning of this reply to the 2nd OA (from pages 6-15).

It may be customary in the art to start treatment (with an antidepressant monotherapy) right away for a suicidal patient, but not with combination treatment. That was also presented as secondary factors in our reply that the PTO ignored. The standard and currently accepted approach in psychiatry is to admit the suicidal patient to a psychiatric unit and observe the patient. In regard of medication treatment both a depressed and the suicidal patients would get the same medication treatment. The only difference (besides the admission to a psychiatric unit) in the management of a depressed and a depressed and suicidal patient is in case of a medical emergency if the patient stopped eating and lost significant amount of weight. In this case ECT is recommended, and in these cases sometimes the patient is even receiving more than one ECT in a single day. This course of treatment is relatively very rare. Simply being suicidal does not constitute to that degree of a medical emergency and the accepted standard is to observe the patient (on the unit) and give an antidepressant monotherapy ("treatment as usual").

The PTO is not a clinician, is unfamiliar with the clinical standards and yet fills a double role to be an expert in that field (and be a "judge"), but is ignoring our teaching. The PTO is disregarding the presented facts and continues with an unconvincing line of reasoning.

The PTO has also left out our inventive steps (e.g. initial treatment, the benefit of the group as it was discussed earlier).

In regards to the low dose, the PTO disregarded our argument in our reply to the 1st OA that included of why the clinician could not reasonably follow the PTO's logic without undue experiment, (including data on the antipsychotic's depressogenic effect), and of how

we did provide extensive guidance and were enabling. Furthermore, we specified the low dose of antipsychotics for our new use.

Included in the PTO's false logic are not only the reasons that lead to malpractice, (see also #1, #2, Figures 1, and 2, #5,) but other reasons as well:

Notably that **if two condition (depression and cognitive distortion) is associated with each other, and in the prior art there is no description that the antidepressants specifically would target the cognitive distortions, than the PTO's conclusion that another medication group could not specifically target the cognitive distortions would not be a convincing line of reasoning.**

To point out this unconvincing line of reasoning let us show two analogies:
In our first analogy the PTO's thinking is like "that if gasoline can propel a car, than hydrogen simultaneously in a hybrid car would be also un-patentable.

The PTO's statement that the artisan would be motivated to use our method as cognitive distortions are associated with depression is similarly unconvincing line of reasoning if there was not a causative factor (mechanism of action) described in the prior art. The PTO has failed to provide that crucial factor that antipsychotics and antidepressants would specifically target cognitive distortion. Therefore the PTO is describing the well known joke in medical research that points out that just because two conditions are associated with each other they may not be causative of the end result: Our second analogy and the well known joke about that is like this: A British a French and a Russian scientist are drinking after a scientific meeting. The British is having Whisky on the rock, the French Brandy on the rock and the Russian is having Vodka on the rock. They all get drunk. The next morning they investigate the reason of their drunkenness and come to the conclusion that the common ingredient in their drink (the associated condition) was ice, and swear that they never going to have another drink on the rock! This points out the unconvincing line of reasoning of the PTO's thinking. (This joke for training purposes makes the point and was actually taught in our medical school!)

Associated and causative conditions are different. While theory may reason of cognitive distortion causing depression, I'm unaware any prior art reference that depression would cause cognitive distortion, or that medication treatment of depression (including the target points) would equal with the (treatment target point of) cognitive distortion.

Even if antidepressants would reduce cognitive distortions that does not mean that another method (antipsychotic or cognitive therapy) could not specifically target and further reduce that condition. If the method is surprisingly new it should be patentable.

The target point in which the SSRI's or the other antidepressants are acting was not through the antidepressants targeting the cognitive distortion but through a specific neurotransmitter. The PTO has failed to show any prior art that would describe that indeed both the antidepressants and the antipsychotic medications as causative factor

are the target point on the cognitive distortions in the depressed, and this is the mechanism of action of both of these classes of medications. The prior art teaching is different from that and focuses on neurotransmitters as the explanation of the supposed mechanism of action of medications.

We on the other hand have described in our theory and reasoning of how these medication classes would target cognitive distortions in case of antipsychotics directly, and in case of antidepressants indirectly but with specific pharmacological action. (The later was described of how the pharmacological, the psychological, and clinical neuroplasticity model of depression interact). The PTO rejected our theories as irrelevant without any clinical explanation on their part.

At the beginning of our reply we have referenced prior art (Miller) as additional evidence of why the PTO lines of reasoning are unconvincing, and indeed other methods like cognitive therapy (or our method) can reduce cognitive distortion after the remission of depressive symptoms (when depression was treated with antidepressant medications). The remission of depressive symptom does not equal with the elimination of cognitive distortion. Therefore new methods like ours can provide further benefit and this is a solution for a long felt need that is patentable.

Our relevant notes about cognitive distortion in our reply to the 1st OA are also explicitly referenced again here.

The PTO acknowledges *(highlighted in italics)* that *"Tollefson does not disclose a method in which the antipsychotic is administered according to the dosage levels disclosed* in instant claims 36 and 95;" and *"Tollefson does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider, or a method wherein treatment is given for preventing suicide."* The PTO also acknowledges that *"Tollefson also does not explicitly disclose a method of treating cognitive distortions".*
The PTO did not use a convincing line of reasoning for obviousness in the prior art, therefore the prior art rejection should be withdrawn.

The **PTO errs** on limiting important clinical and inventive steps only to **"various motivations"** as we have discussed that **under #8-9**.

Also notable that the PTO cites a class of medications called SSRIs ("**Specific serotonin reuptake inhibitors"**). (#6 discussion).
See also Reply O.

The low dose issue would be revisited in the next box under Reply R (in addition to Reply J).

It is also notable as an observed and repeated pattern by the PTO examiners that the examiners condition their reasoning, but these exact conditions they set in their line of reasoning are unconvincing. For example, if the reason of "because" that is conditioning invalidates the entire sentence as it is false (unconvincing) then

consequently the PTO's conclusions would also be false (unconvincing). For example, if that exact step that the PTO suggests is deviating from the standard of care, and thus would lead to malpractice then the PTO reasoning cannot be convincing. In other words, the PTO's reasoning is false and not convincing if it does not follow the thinking pattern of the one skilled in the art. If the examiner conditions his reasoning and the conditioned (supposedly) supporting part of the sentence is false, and/or if this unconvincing line of reasoning (false logic) is carried over and over again, than the end result and the conclusions including the basis of the claim rejections are also false!

Here the PTO came up with another such example: "One of ordinary skill in the art would reasonably have expected success in administering treatment as soon as possible to prevent suicide because suicide is known to correlate strongly with depression, and **because treating a subject for a serious condition as son as possible is a generally recognized practice in the art**."
The explanation was given in the second paragraph of this box: **It may be customary in the art to start treatment (with an antidepressant monotherapy) right away for a suicidal patient, but not with combination treatment**. That was also presented as secondary factors in our reply that the PTO ignored. ... (Seee also Figures 1, 2, and 3).

Page 28
Response to Argument: Applicant's argument, filed September 22, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that Tollefson's disclosure is non-enabling because Tollefson's method is inferior to other prior art methods for treating rapid-onset depression known at the time. In particular, Applicant claims that, "while an inferior product can be patented, a drug that is harmful cannot be patented, and Tollefson failed to show that analysis." However, Applicant does **not** demonstrate that the method of Tollefson (and **thus Applicant's own method**) is in fact **harmful**, as opposed to merely being inferior to other treatment approaches. 117 order to be genuinely harmful, Applicant would need to show that there exists no case in which Tollefson's therapeutic method would be preferable to no treatment at all. **While the drugs used have side effects, they are not so dangerous as to preclude any utility whatsoever, as evidenced by their use for other clinical indications**. Therefore Tollefson's therapeutic method is considered to be enabled and legitimately cited as prior art.

Applicant further argues that **depression is not included within the scope of cognitive distortion and cannot be equated with cognitive distortion**, and that either one can exist without he other. However, **the fact that these two terms are not identical does not preclude a method of treating cognitive distortion by treating depression**. For

Page **29**

example, Applicant states that, "cognitive distortions may contribute to or worsen a number of illnesses like addictions, smoking, pathological gambling, impulse control disorders, anger, with consequent relationship conflicts, major depression, anxiety disorders, . . ." Therefore a method of treating major depression can reasonably be considered a method of treating the symptoms of cognitive distortions. Furthermore,

two disorders need not be exactly equivalent for the relief of one to relieve the other. *While cognitive distortions and the risk of suicide may still linger and* **require further treatment**, their magnitude and impact can be lessened by treating the associated depression, and this procedure would reasonably be considered a method of treating the cognitive distortions.

Applicant also argues that Tollefson does not disclose a **low dose** for any of the disclosed antipsychotics. In the absence of an actual dosage range, the term, "low dose" as recited in the instant claims is **so broad and indefinite** as to provide no meaningful limitation to the scope of the claims. As regards the specific doses recited in instant claims 36 and 95, Applicant argues that the dosage levels of the claimed invention are not obvious in view of Tollefson because the claimed invention functions by a different method from the prior art and one of ordinary skill in the art would not know that the low doses of the claimed invention are useful for this method. However, it is noted that the **claimed dose ranges for olanzapine and risperidone overlap with the preferred dosage ranges disclosed by Tollefson**. For these active agents at least, Tollefson clearly suggests using an especially preferred dosage of antipsychotic falling within Applicant's claimed range. Therefore, **the claimed dosage levels for these two**

Page 30

agents are not considered to be so much lower than the prior art as to render the invention non-obvious.

For these reasons, the rejection is deemed proper. Because Applicant's amendment necessitated this rejection, the rejection is made **FINAL.**

Reply R: The PTO's statement of "Applicant does **not** demonstrate that the method of Tollefson (and **thus Applicant's own method**) is in fact **harmful**," is an erroneous (unconvincing) logic twice in one sentence!, as it was discussed under #1-3 #9 and Figures 1-3. The following underlined parts were also discussed above at the same places.

The PTO's statement that follows is equally unconvincing (false) and clinically unsubstantiated conclusion: "**While the drugs used have side effects, they are not so dangerous as to preclude any utility whatsoever, as evidenced by their use for other clinical indications**. Therefore Tollefson's therapeutic method is considered to be enabled and legitimately cited as prior art." The clinical decision making and the evaluated risks are based on different steps, and the PTO cannot assume that just because the antipsychotic is used in a psychotic depression, where the antipsychotic specifically targets the psychosis, than without reasons that should also be used when the psychosis is not present. The same is true for treatment resistant depression as we have disclosed this in our utility (page3 lines 21-24): "Nierenberg (Nierenberg. A. A., 1992) had noted that the cause of treatment-resistant depression may be an unrecognized psychosis, that may explain – at least in part – of why the "treatment-resistant" depression group improved with the addition of an antipsychotic medication." Furthermore, Tollefson never ever claimed his method for non-TRD patients as initial treatment.

The erroneous nature of the PTO's above conclusion is further supported that the PTO examiner himself had acknowledged at page 16 that "**antipsychotic drugs are only known to be of benefit from patients having a psychiatric disorder involving psychosis or psychotic-like symptoms.**" So the PTO logic of relying on that "it is logical" to use the combination treatment when there is no known indication for it and therefore the PTO's statement that Tollefson's method would be "enabling" for any or all other use that was not even described in that prior art is simply a false (erroneous) statement and does not follow the clinical steps or any convincing line of argument whatsoever.

The bolded parts on the PTO's unconvincing line of reasoning about cognitive distortion were discussed under **Reply Q** (q) above (and in our reply to the 1st OA), and in **Reply O** where the PTO's false statement was pointed out: The PTO has failed to show any prior art stating that "**certain drug therapies can affect the cognitive distortions that predispose a subject to suicide or to relapse in smoking cessation**," on page 22. This was **not** known in prior art, as the mechanism of actions of any drugs. The mistake for the PTO to assume that, or suggest that assumption is incorrect.

The same unconvincing line of reasoning applies to the PTO's statement of "Therefore a method of treating major depression can reasonably be considered a method of treating the symptoms of cognitive distortions." There is no proof in the prior art on a mechanism of action (a causative factor) for how the antidepressants or the antipsychotics would work on cognitive distortions. Therefore the assumption is incorrect and **Reply Q** (q) and our argument at the beginning of this reply to 2nd OA applies.

The PTO is acknowledging on page 29 that "*While cognitive distortions and the risk of suicide may still linger **and** **require further treatment***" is exactly what we were saying about in the analogy of a hybrid fuel car. Our method can be still patented **and the PTO with the above statement implicitely acknowledged that!**

Furthermore, the PTO ignores our extensive proofs about the difference of cognitive distortion and depression, and states falsely "this procedure would reasonably be considered a method of treating the cognitive distortions" without providing a logical line of evidence overriding the above standard of care and research requirements in Reply Q (q) & Reply O.

Furthermore the PTO is also **disregarding our specific theory and reasons** as we have mentioned that in Reply Q (q) and in the reply to the 1st OA. The Wands factors *and Genetech,* 108 F.3d at 1366, also applies to our case, that sates that, "a patent is not a hunting license. It is not a reward for search, but compensation for its successful conclusion." And "patent protection is granted in return for an enabling disclosure of an invention, not for vague intimations of general ideas that may or may not be workable." (We emphasize here the underlined parts!)

The **low dose** issue had been discussed before in our reply to the 1st OA; here under 10d) of page 12-13; and in **Reply J, & Q (q) !** If the PTO talks here about cognitive distortion than the PTO's generalization for a different and that particular patient population is even more exaggerated and incorrect. However, either way, we have provided new use (non-TRD, non-psychotic depression).

At page 26 the PTO repeats that "It would have been obvious to one of ordinary skill in the art to administer the drugs in the methods of Tollefson et al. at the dosages describes in instant claims 36 and 95."

The PTO states that "the claimed dosage levels for these two agents are not considered to be so much lower than the prior art as to render the invention **non-obvious.**" The fact is left out that we have provided new use (non-TRD, non-psychotic depression, and for initial treatment) and that the prior art to use our new use was not enabled or obvious. **Critical** differences regarding low dose and the **preferred range in the prior art**, that (in case of olanzapine) **is the 33% higher than the maximum FDA approved dose was disregarded** in our argument by the PTO. **Critical** differences as a consequence from the prior art dose range like on the antipsychotic's depressogenic effect at high doses, (or at high doses the

treatment emergent anxiety and akathisia [that can lead to treatment emergent suicide]) was also disregarded by the PTO in our reply to the 1st OA. It is true that differences in dose is generally will be obvious unless there is evidence indicating **that it is critical**. We have provided attention to the importance of low dose, and the critical differences like the depressogenic effect of the antipsychotic and the EPS side effects (akathisia). [see page 2 lines 6-9 and page 4 line 19 of utility]. The PTO's line of reasoning therefore by ignoring our argument was not convincing as we have shown here. (See also complete Patent book p. 220)

See also 2nd reply #4, J & Q(q).

It is hereby presented that based on our description **the skilled in the art would readily be able to determine case by case the concept of what the low dose is.** (The medical/psychiatric profession would rely on their clinical judgment, on our guidance on the low dose being about 1/3rd of the usually administered dose for psychotics (and the target dose is known in the PDR and in the art in that regard). Furthermore we have mentioned that there are equivalent dose tables for typical antipsychotics, and the skilled in the art would be able to use the same knowledge without undue experiments for new medications from our examples we have given on specific and known substances. Furthermore it is presented that for the skilled in the art – specifically with our guidance – the low dose concept cannot be infinite. High dose exceeding the conventional dose for psychosis is not a low dose, so it is limited from the upper end. Zero (or doses close to it) would be ineffective so that the dose should be greater than zero, so **the low dose is bracketed**. The preferred low dose is usually about 1/3rd of the target dose for psychosis and is not a conventional target dose for psychosis, or a dose exceeding that. This is with a note that sometimes doses similar to the target dose given for psychosis may be still effective, (with exception from this when EPS and other side effects occur).

> Page 9 lines 10-25 of the utility: "In the method of the present invention, the dosage of the antipsychotic drug should **be around approximately one-third (1/3) to the average dose** of the amount normally prescribed. However, a lower than average dose is preferred for most cases. At times minimal dose can be expected to be sufficient, like for quetiapine 25-50mg, (if needed raised up to 300-400 mg q.d.), for risperidone 0.5-1mg (if needed raised to 2-4 mg q.d.), for olanzapine 2.5 mg-5mg, (and at times used at 10 mg q.d.), or for ziprasidone 10-20mg (at times at 40mg), and most likely, for aripiprazole 2.5-10 mg q.d. or less; (if needed given at 15mg q.d.) as an example.
>
> It should also be understood that these doses are not fixed, and a lower dose may be effective for some, but not for others. In the case of the atypical antipsychotics and dopamine system stabilizers, a higher dose (similar to the doses given for psychosis) may be effective in the prevention of suicide. **The exceptions from this are the doses when EPS** and other side effects **occur**. However, it is best to expose the patient to the least amount of effective medication. In addition lower doses may have other benefits as well."

It is notable as we have discussed in our reply to the 1st office action, that the PDR gives target dose for the antipsychotics (and we have also discussed that the target doses in the literature is described often as higher than the PDR doses. These should be known to the artisans.

> Page 14 lines 28-31, page 15 lines 1-2: "If typical (or conventional) antipsychotics are used as adjunct to antidepressants a low dose should be given. The doses of the typical antipsychotics are also often given in "chlorpromazine equivalent" doses. (See e.g. conversion charts at DeBattista, C. et al 2003, p91; Jenkins S.C. et al 1990, p134). A low dose of an antipsychotic would mean a chlorpromazine equivalent" dose of 25-50mg, or up to 100-150mg q d."

The hypothetical examples also supported the low dose concept. (See also Reply J & Q (q),).

The PTO's line of reasoning errs on that we have specifically argued the difficulties that the clinician may encounter with the higher doses, and the depressogenic effects form the antipsychotic medications had been described in the prior art as we were also referencing them in our utility (page 2 lines 6-9). We also draw attention to EPS and akathisia problem at higher doses (see above page 9 line 10-25 bold underlined part and page 4 line 19 of our utility. Therefore a lower dose range is **critical** and non-obvious specifically when "the prior art's preferred dose range for olanzapine –their own drug - **includes a top range that is up to 33% higher than the FDA approved dose!**" (as we have stated ""For risperidone the preferred range is relatively still high and not a low dose.") The PTO left out our argument in this regard, from page 66 lines17-19, (of reply to the 1st OA) in particular that the artisan – without undue experimentation would have encountered difficulties in adjusting dosages and facing the potential of getting an opposite, a depressogenic effects form the antipsychotic medications or treatment emergent anxiety and akathisia linked to treatment emergent suicide. In the PTO's reply that was not addressed. A critical and different dose range can be still patented within the range of the prior art description. However, here in our claims there are additional new limitations (and as we have shown the prior art is not enabling in regards to our claims).

In the phone interview with the PTO (after the 2nd OA) we mentioned of considering leaving the low dose out if it continues to be a problem. The PTO stated that every little difference from prior art may help getting approval.

Page 30

Claims 8, 19, 23, 27, 31, 78, 82, 86, and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Tollefson (PCT international publication W099161027) in view of Kelleher et al. (Reference included with PTO-892) The disclosure of Tollefson is discussed above. Tollefson does not disclose a method in which the atypical antipsychotic agent is aripiprazole.

Kelleher et al. discloses a number of atypical antipsychotics. One of these drugs is aripiprazole, described as **an experimental** atypical antipsychotic **which is a partial agonist against D2 receptors**. (p. 257, right column, third paragraph) It should be noted that Kelleher appears in volume 16, no. 4 of the publication CNS Drugs, which is the April 2002 issue, and thus prior art against the instant application.

It **would have been obvious** to one of ordinary skill in the art at the time of the invention to use aripiprazole as the atypical antipsychotic in the method of Tollefson et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Kelleher et al. reveals that aripiprazole is useful for the same purposes as other atypical antipsychotics but with a reduced side effect profile. One of **ordinary skill in the art would reasonably have expected success** because Tollefson already discloses a method using any atypical antipsychotic agent generally.

Page **31**

Thus the invention taken as a whole is ***prima facie* obvious**. Because Applicant's amendment necessitated this rejection, the rejection is made **FINAL**.

Reply S: It needs to be noted that we do maintain our arguments in the reply to the 1st OA. The PTO examiner brings up Kelleher's publication on aripiprazole, being described as **an experimental** atypical antipsychotic **which is a partial agonist against D2 receptors.**

The bolded sections demark of why one of ordinary skill in the art would **not** reasonably have expected to use and substitute that drug for Tollefson's disclosure (and for our new use). First of all in order to prescribe an experimental drug not yet FDA approved, one needs to have special permission and clearance from the FDA and/or from the institutional review boards and from the patients to use an experimental medication. So the average artisan would have not been able to substitute Tollefson's technique with aripiprazole at the time of our invention. Second, the average clinician is well aware of the difference between an antagonist and a **partial agonist** (against D2 receptors). The two classes of medications can behave distinctly differently, as it is also understood from the example of morphine that currently you would not want to (that is you cannot) prescribe morphine to a morphine addict and give that patient a buzz or "high" and with that action support the patient's addiction. The same applies to heroin, you would not supply heroin to a heroin addict. That would be malpractice and you would loose your medical license and FDA number over that. A **substance of partial agonist or of partial agonist and antagonist activity behaves differently** and with new data supporting this some of these compounds can be used in the addiction field. So (based on the "prototype" morphine or morphine analogy – even if the action is on a different receptor) the average artisan would or could be leery about using a partial agonist and antagonist or a partial agonist in lieu of an antagonist. For these reasons the average clinician at the time of our invention would not automatically substitute and use the two classes of drugs with each other. **Third, and most importantly**, as we have described above, the Tollefson reference was **not disclosing** as to our invention, and it was only the PTO's unconvincing line of reasoning (false logic) (also leading to malpractice) that was stating that that prior art was enabling. **Without adequate enablement the prior art rejection needs to be withdrawn**. The secondary factors were also ignored. So using aripiprazole was **not obvious at all** for the purposes of our claims.

Page 31

Claims 1-2,4-6, 9-1 1, 1 3-1 4, 37-38,42,48, 51, 53-64, 66, 69, 70, 73, 96-1 04, and 1 09-1 1 8 are rejected under 35 U.S.C. 103(a) as being obvious over Faour et al. (US patent application, 091728276, Pub. No. 200110048943 Al, patented as US patent 6572890, cited in PTO-1449) Faour et al. discloses, "a method of treating **depression, anxiety,** and or psychosis in a mammal, the method comprising administering an osmotic device which provides a controlled release of VFX [Venlafaxine, a selective serotonin and norepinephrine reuptake inhibitor] from its core and a rapid release of an anti-psychotic agent from an external coat," (p. 2, left column, paragraph 0020) anticipating instant claims 1-3, 9, 11, 13, 14, 37, 42, 48,49, 51, 53, and 54. This osmotic device is meant for oral administration, anticipating instant claim 38. Various embodiments of the invention of Faour et al. include a number of atypical antipsychotic drugs, (p. 2, left column, paragraph 0022-0023) including those recited in instant claims 5, 6, and 10, for example. Faour et al. does not explicitly disclose a method of administering the claimed treatments as an initial treatment, as soon as possible, or upon presentation to a physician or other health care provider.

It would have been obvious to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Faour et al. as an initial therapy and or to administer it as soon as possible. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Faour et al. already

Page **32**

discloses the treatment to be useful as a treatment for depression generally, and because it is standard practice in the art to administer a therapy promptly once it is indicated. One of **ordinary skill in the art would reasonably have expected success** because choosing a particular therapeutic regimen from among the various options

available in the prior art is within the routine and ordinary level of skill in the art. Thus the invention taken as a whole is prima *facie* obvious.

Reply T: The PTO disregards that Faur described only a delivery method and was not enabling as for our claims. This was described in our reply and under #3 above along with the same arguments as against the Tolefson reference. (#1-5, #8-9,).

The new line of argument regarding Faour that was brought up by the PTO at the phone interview (after the 2nd OA) and was discussed at length the beginning of this reply to the 2nd OA (page 6).

The underlined following parts were discussed in earlier parts, (about Tollefson and Chappell), and the examiner's statement, the bolded part is also not supported by the secondary factors that the PTO left out of any consideration. The PTO therefore showed a unconvincing line of reasoning that is not supported by facts and the secondary factors. [see also reply Q (q).]

Page 32
Response to Argument: Applicant's argument, filed September 22, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that one of ordinary skill in the art could not have used the method of Faour et al. to treat non-psychotic depression because use for this indication was not adequately disclosed or enabled by Faour et al. However, Faour et al. does disclose **how to make the disclosed dosage form and which patient population (those suffering from depression) to administer it to. Therefore it is considered to disclose how to make and use the claimed invention.** One of ordinary skill in the art **would face no difficulties in practicing this method based on the disclosure of Faour** et al. Applicant has provided **no** evidence which would demonstrate that the disclosure of Faour et al. is not enabling or that the invention described therein is not operable. Therefore the disclosure is judged to be enabled and the invention operable. Furthermore, the fact that Faour et al. discloses embodiments directed to the treatment of depression or anxiety comorbid with psychosis does not prevent it from rendering obvious a method of treating non-psychotic depression. *An embodiment of the prior art need not be a preferred embodiment in order to anticipate or render*

Page 33

obvious the claimed invention. **Although no risk-benefit analysis or other specific guidance is given for the treatment of non-psychotic depression, the art is sufficiently predictable as regards known antidepressants and antipsychotic agents,** as discussed at length by Applicant in his arguments with respect to the enablement of the claimed invention, that one of **ordinary skill in the art would have been able to reliably use a known agent for these indication even without a detailed study** providing exhaustive detail as to the effects in each and every possible indication.

Applicant also argues that Faour et al. does not disclose a low dose for any of the disclosed antipsychotics. In the absence of an actual dosage range, the term, "low dose" as recited in the instant claims is so broad and indefinite as to provide no meaningful limitation to the scope of the claims.

For these reasons, the rejection is deemed proper. Because Applicant's amendment necessitated this rejection, the rejection is made **FINAL.**

Reply U: The PTO argument does not stand scrutiny and is showing again a false (unconvincing) logic that deviates so much from the clinical standard. With the first bolded parts the PTO disregards important and crucial inventive and risk analysis steps. (see also

e.g. #1-5, Figures 1-3). So the PTO's conclusion that the clinician would have faced no difficulties in practicing the invention is strongly incorrect when we have pointed out that the clinician skipping steps would commit malpractice. The PTO left out and did not reply to that argument. For similar reasons and for the reasons described in the PTO's statement is also **incorrect** when they state that "Applicant has provided **no** evidence which would demonstrate that the disclosure of Faour et al. is not enabling". This is particularly not true with the new information provided here at pages 6-15. The truth is simply that the PTO disregarded our arguments and the secondary factors or that the PTO did not read them or that the PTO was not knowledgeable – despite of our teachings – of the required clinical decision making steps. Again the PTO cannot assume that the artisan would want to commit malpractice. In addition, - as mentioned - at (pages 6-15) at the beginning of the reply to the 2nd OA we have provided additional detailed information on why the Faour reference is not enabling.

The examiner shows with the following arguments that the PTO is unfamiliar with the rules of how a drug can be used off label: ("use[ing] a known agent for these indication even without a detailed study"). **The artisan can only use an FDA approved agent for a new indication off label if there are sufficient reasons and guidance available that is if there is an enablement**. Without that the clinicians face malpractice. (I cannot use megadoses of aspirin off label to experiment on patients if it is good as an anticancer agent if there is no substantial good reasoning to show that that step would benefit the patient overriding the risk, and would be more beneficial than other available alternatives.) So the PTO's logic and statements is simply unconvincing and unsubstantiated that:

1) without the risk/benefit/alternative analysis steps and
2) without enablement for the reasons to use the combination
3) for new indication
4) that deviates from the standard of care
5) specifically when there is a strong teaching against of using the method
6) and **if that is within a larger diagnostic group**, (requiring further inventive steps for enablement),

then the one of ordinary skill would cross these barriers (and face malpractice).

Similarly, the PTO's line of reasoning that the **no** guidance in the prior art would render our invention enabled that is that the "art is predictable as regards known antidepressants and antipsychotic agents" that is (as implied) **for our new indication (!) is also unconvincing**. The artisan cannot skip mandated clinical steps. The above PTO statement would also contradict the PTO's own earlier statement (page 16) (that we mentioned under Reply N) when the PTO acknowledged that the antipsychotics are known only for psychosis related illnesses.

The PTO's arguments are repeatedly and bona fide unconvincing. The PTO is building

upon unconvincing arguments again and again while disregarding our arguments the routines of the standard clinical care, as well as the secondary factors. **It is not surprising that the final conclusions by the PTO are also false.**

It should be noted, that even for FDA approved drugs for the approved indication, an off label use for higher than the approved dose, can be risky and requires plenty of good documentation for that reason. That has to include a detailed risk/benefit/alternative analysis. This applicant (at his or at his former workplace) had been reminded by the hospital's chief pharmacist several times even for that same approved indication but for exceeding the FDA approved dose on atypical antipsychotics that "if adverse event occurs you are on your own even if the pharmaceutical representatives or others advocated that". This is despite of the fact that atypical antipsychotics have plenty of backup support in the literature for that higher dosing and for the benefits of that dosing in certain patients. In contrast, for a new breakthrough invention – that by definition is not obvious – and which invention is presented in a patent application without supportive experimental data (like according to the PTO any of the Faour, Chappell, and Tollefson references) for a broad use of depression [that by the PTO's explanation should include the subpopulation of MDD non-TRD, non-psychotic subgroup] the documentation of (or thinking of) the risk benefit/alternative analysis is absolutely essential! How could you otherwise enable a method? **None of the prior art** (patent applications) referenced by the PTO – or any other prior art that we are aware of – **had that reference to the risk/benefit/alternative analysis**; (and without that – **without explicit guidance) these prior art references simply cannot be enabling for the purposes of our claims!** We on the other hand went an extra mile of providing extensive guidance, including specific reference to the risk/benefit/alternative analysis.

In addition as we have shown at page 27 under "another lines of reasoning" none of the prior art documents were in the possession of our invention.

The low dose issue was discussed before in our 1st reply and Reply J.

Page 33

Claims 1-2, 4, 7, 9, 11-15, 37, 38, 42, 48, 51-62, 70-74, 96-105, and 109-1 18 are rejected under 35 U.S.C. 103(a) as being obvious over Chappell et al. (US patent application 101001827, Pub. Number 200210094986 Al, of record in previous office action) Chappell et al. discloses a method of treating depression, anxiety, or psychosis in a mammal by administering a combination of an antidepressant, **a D4 receptor antagonist, (an antipsychotic)** and a pharmaceutically acceptable carrier. (p. 1, left column, paragraph 0002) General types of antidepressants which can be used are listed in paragraph 0021 and include norepinephrine reuptake inhibitors, serotonin

Page **34**

reuptake inhibitors, and monoamine oxidase inhibitors, among others, as described in instant claims 11-13. Norepinephrine reuptake inhibitors which may be used are listed in paragraph 0023 and include clomipramine among others, as in instant claims 14 and 15. The compounds used in this invention may all be administered orally, as described by instant claim 38. (p. 22, paragraphs 0460-0462) Chappell et al. does not explicitly disclose a method of administering the claimed treatments as an **initial treatment**, as soon as possible, or upon presentation to a physician or other health care provider. It would have been **obvious** to one of ordinary skill in the art at the time of the invention to administer the therapy disclosed by Chappell et al. as an initial therapy and/or to administer it as soon as possible. One of ordinary skill in the art would have

been motivated to practice the invention in this manner **because** Chappell et al. already discloses the treatment to be useful as a treatment for depression **generally**, and because it is standard practice in the art to administer a therapy promptly **once it is indicated**. One of ordinary skill in the art would reasonably have expected success because choosing a particular therapeutic regimen from among the various options available in the prior art is within the routine and ordinary level of skill in the art.

Thus the invention taken as a whole is *prima facie* obvious.

Reply V: The first bolded and underlined parts supports our argument under #6.

The examiner errs due to unconvincing line of reasoning and skipped inventive steps on rendering initial treatment obvious. (See #4, and #5 for example). As discussed a mentioning of a broader diagnostic category would not render other subcategories obvious against the standard clinical care without reasons and specific guidance and enablement. (see #3). Explanation of why to skip steps to avoid malpractice has to be made in order to enable a method. Thus the prior art does not make our invention obvious.
There is also a logical problem with the PTO's following statement: "because it is standard practice in the art to administer a therapy promptly **once it is indicated**." The point is once it is indicated, and as we have shown by the secondary factors, at the time of our invention the combination therapy **was not indicated (!)** for the use of our claims! [see also Q (q)]. Therefore the whole PTO statement is incorrect.
We have also discussed the above under #1-3 and specifically under Figure 2 (in addition to the 1st reply).

We have addressed in Reply Q (q) the PTO's pattern of falsely conditioning their reasoning. The exact same applies here with the above example.

Page 34

Response to Argument: Applicant's argument, filed September 22, 2007, as applied to the above rejection, has been fully considered and not found to be persuasive to remove the rejection. Applicant argues that Chappell et al. does not provide sufficient guidance or enablement to allow one of ordinary skill in the art to practice a method for treating non-treatment-resistant, non-psychotic depression. However, the **art is**

Page 35

sufficiently predictable as regards known antidepressants and antipsychotic agents, as discussed at length **by Applicant** in his arguments with respect to the **enablement** of the claimed invention and the ability of one of **ordinary skill in the art to practice off-label administration of known antipsychotic agents**, that one of ordinary skill in the art would have been able to reliably use a known agent for these indication even without a detailed study providing exhaustive detail **as to the effects in each and every possible indication**. One of ordinary skill in the art would have recognized how to practice the claimed invention given the **disclosure** by Chappell et al. that these pharmaceutical combinations are suitable for the treatment of depression, **including those cases of depression demonstrating neither psychosis nor treatment resistance**.

Applicant also argues that Chappell et al. does not disclose a low dose for any of the disclosed antipsychotics. In the absence of an actual dosage range, the term, "low dose" as recited in the instant claims is so broad and indefinite as to provide no meaningful limitation to the scope of the claims.

Reply W: The PTO repeats the mistakes made in their logic as discussed under **Reply U.**

The examiner shows with the following arguments that the PTO is unfamiliar with the rules of how a drug can be used off label. **The artisan can only use an FDA approved agent for a new indication off label if there are sufficient reasons and guidance available that is if there is an enablement.** There needs to be a reason of using the combination for new indication, there needs to be a risk/benefit analysis step adequately disclosed, and the clinician also must to compare the treatment to the current standard of care and teaching against that method. Only if all of these steps are enabled can the artisan use the technique. None of the prior art was enabling for these reasons.

Therefore the PTO incorrectly names it a "disclosure" of a mere mentioning of the drug combinations by Chappell specifically when it is not used for the same indication. No guidance or not even a mentioning was used in the Chappell reference of our diagnostic criteria even if it falls within that broad diagnostic category. [See also #4 "another line of reasoning 1)-4)]. **For our more restricting diagnostic group – in order to be able to deviate from the standard of care – additional clinical and inventive steps should be used.** (See #3). This was not conceived by Chappell as being even a remote possibility for their invention. Much less, the Chappell reference did not disclose any guidance of how the clinician can overcome the required barriers to avoid malpractice and use their method off label. The Chappell reference also not discloses any lines of argument for initial treatment (or to use that method for substantially all of said patients within our group of diagnostic category). On the other hand we have shown the PTO's line of reasoning was unconvincing. The PTO did not answer to these arguments brought up in the reply to the 1st OA, which was more specifically spelled out as for even to be understandable by a lay person in Figures 1-3, and #1-5.

The low dose issue was discussed before in our 1st reply and Reply J.

Page 35

Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell et al. (US patent application 101001827, Pub. Number 200210094986 A1 , of record in previous office action) The disclosure of Chappell et al. is discussed above. Chappell et al. **does not disclose a method in which the antidepressant is ketamine.**

Berman et al. discloses that ketamine exerts antidepressant effects in human patients. (p. 351, second paragraph, right column, p. 352, left column, last paragraph, p. 353, right column, first paragraph)

Page **36**

It would have been **obvious to one of ordinary skill in the art at the time of the invention to use ketamine as the antidepressant in the method of Chappell** et al. One of ordinary skill in the art would have been motivated to practice the invention in this manner because Berman et al. **reveals that ketamine is useful for the same purposes as the antidepressants recited by Chappell** et al. One of ordinary skill in the art would reasonably have expected success because Ketmaine is already known to be useful as an antidepressant.

Thus the invention taken as a whole is prima *facie* obvious. Because Applicant's amendment necessitated this rejection, the rejection is made **FINAL.**

Reply X: The PTO again reveals that they are unfamiliar with the clinical decision making steps. The artisan needs to go over risk benefit analysis. Ketamine is known to have a

severe psychomimetic (hallucinatory) side effect as it well known in the art and is also disclosed in our prior publication (Migály, P., Károvits, J., Jakab, T., Gaál, K. Effects of ketamine anaesthesia and stress-reducing psychological methods on surgery patients. In: Stress and Emotion, Vol. 14, Spielberger, Ch., Sarason, I., Kulcsár, Zs., Van Heck, G., (eds.) Hemisphere Publ., New York, 1991, 215-224. and only as a mention: Migály, P., Jakab, T. [Psychomimetic side effects of ketamine anaesthesia and the mechanism of action of drugs reducing these effects. Hallucination and neurotransmitters: a review]. (Hun.) Orv. Hetil., 1986, 127, 1201-1206.) Therefore, the **average artisan without a good enough reason would not have wanted to expose the patient to these unwanted and disturbing side effects as a mere substitute** of the Chappell reference, even if it is disclosed by Berman having an antidepressant effect in humans – without our own specific guidance and risk benefit analysis that was not in any of the referenced publications. As we stated in our provisional application that it is the "prevention of suicide" (using here the medical meaning) that is the crucial factor in the risk/benefit/alternative analysis. Without that analysis - which was not provided neither in Chappell nor in the Berman references, - the artisan would not have been able to substitute ketamine for these drugs.

> (It is of a special note that claims 106-108 recite 55, 57 or 61 which indirectly depend from claim 1, and 2 or claim 3, where the treatment is given for resisting suicide along with other limitations. Therefore the target is for a different indication than reducing the hallucinatory side effect of ketamine. Furthermore, in accordance with our hypothetical examples the treatment with the antipsychotic is not limited to a single dose, but given as a course of treatment over time. This is also in accordance with our provisional application. Therefore our claim as understood in the art would not conflict with prior art.)

Second, ketamine is an anesthetic. The PTO is right in assuming that the mere intramuscular (i.m.) or intravenous (i.v.) administration of a drug would not cause a problem since many of the antipsychotics can and are given i.m. or i.v.. This applicant also gave i.v. antipsychotic in ICU for a patient with psychosis. However, with all other concerns the question is not whether the PTO thinks that the average artisan would substitute ketamine for Chappell's method (or for ours) but by looking the secondary factors 5 years later whether they did or not. The answer for that indication is a clear no! So the average artisan would not have substituted Chappell's method with ketamine at the time of our invention.

Third, the Chappell reference was not enabling for the purposes of our claims – **as we have discussed above under #1-5.**

So the conclusions by the PTO are false.

Page 36-37

Conclusion

No claims are allowed in this application. Applicant's amendment necessitated the new ground(s) of rejection presented in this Office action. Accordingly, **THIS ACTION IS MADE FINAL.** See MPEP § 706.07(a). Applicant is reminded of the extension of time policy as set forth in 37 CFR 1. I3 6(a).

... (deleted parts)

... In no event, however, will the statutory period for reply expire later than SIX MONTHS from the date of this final action. ..... (deleted parts)

Eric S. Olson Patent Examiner

Anna Jiang supervisory Patent Examiner

Reply Y: Conclusions can only lead to false results if they are based on unconvincing line of reasoning (false logic), and by disregarding the presented facts and the secondary factors.
Therefore the PTO erred with their conclusions.

Please see our note in Reply Q (q), about that if the PTO is conditioning it's line of reasoning but the conditioning "because part" does not stands the scrutiny of the one ordinary skilled in the art - because that part is unconvincing (illogical or is disregarding facts and reality) or is leading to malpractice, - than the PTO's consequent and final conclusions are also unconvincing (erroneous). As we showed the prior art arguments need to be withdrawn. Disregarding our theory or reasoning as well as the secondary factors or our extensive arguments would undermine a fair evaluation from the PTO, and would only create a false, off reality based logic (since things were disregarded) on lack of enablement or on maintaining obviousness based on prior art. (Please also refer back to our reply to the 1st OA, especially on the strong supporting secondary factors). Thank you.

Reply Z: -- Very Important -- We are fulfilling our obligations to inform the PTO of any new information brought to light with also submitting the required information disclosure forms. **We think that it is best if discussion of prior art brought to our attention by an opposing European attorney* (not the patent office) (expressing some alleged concerns) would be incorporated herein as an integral part of this reply:**
(*The opposing European attorney (not the patent office) has submitted his observations to the European patent office). See copies of the non-PTO prior art documents in the enclosure.

Please also see Figures 1-3 discussed previously as it also relates to the documents discussed below.

Document from Tollefson and Eli Lilly company EP 0966967 A2.
The opposing European attorney's (not the patent office's) allegation leaves out the fact that - without the risk benefit alternative analysis and without explicit discussion of how this document would overcome the deviation from the standard of care and use that technique for non-psychotic, non-treatment resistant depression, - this document (EP 0966967 A2) cannot be enabling. The above document would not be enabling for deviating from the standard of care for our new use (and) as for initial treatment. As discussed above, that enabling is lacking and the clinical trials do not provide any evidence for non-treatment resistant cases, in fact it specifically mentions only a patient population with treatment resistance. Going into a theoretical case that even if they would have disclosed and discussed a research study involving non-treatment resistant patients they would still have to go through an analysis that we went trough that why the benefit of the group would substantiate to override the currently used and known risk benefit analysis. We have quoted from our provisional application:

> **"One could speculate that if using the SSRI-atypical neuroleptic combination would increase the response rate of treatment-resistant depression, then the percentage rate**

for improvement would be also higher if given for everybody who is clinically depressed, that is without separating the 'responders' from the 'non-responders'.

This speculation is probably correct, **but by itself would not substantiate the added risk using the neuroleptics.** With this rationale, the two step strategy would seem still to be the logical step, to treat the depressed patients with antidepressants first, and reserve other strategies for the treatment-resistant group only. In the argument to consider, or start using the combination treatment right away in all those who are clinically depressed, **it is the decrease of suicide rate that is the paramount important factor.** ..."

So they would have needed to go through a risk benefit analysis in this regard even if they would have had patients disclosed in their trial with non-treatment resistant depression. **None of those conditioned ifs were there** however in the Tollefson references.

We on the other hand did provide these steps and enablement. Deviating from the standard of care or not doing risk benefit alternative analysis is an automatic malpractice as it is also known in the risk management field within the medical art. The above mentioned document therefore could not anticipate our invention, and in fact there were inventive and additional steps involved.

Document from Tollefson and Eli Lilly company EP 0958824 A2
The opposing European attorney (not the patent office) misquotes the applicant: Document 2's (page 2 [0001] describes their method for treating refractory depression or partial responders. The description of partial responder is less then 50% as was also stated by the opposing European attorney. However, the opposing European attorney errs with his following line of argument [page 7 (7.2) lines 6-7], as our claims did not encompass the non-response defined as less than 25%. (See also our utility page 10 lines 11-15; followed by lines 16-21 that the opposing European attorney disregarded):
"It is possible to have a response to an antidepressant treatment (i.e. better than a partial response or non-response), but still have residual symptoms, and not a full recovery. Therefore the combination may also be effective to treat residual symptoms of depression (which is a separate entity and not equal to partial response), to achieve full remission as a goal. In this case the risk/benefit analysis of giving a medication combination is also different from TRD." Thus that patient population is encompassing the patient population that document 2 (EP 0958824 A2) did not claim, the better than 50% (and not the less than 50%) responders. Additional step(s) a different risk benefit analysis was also revealed, along with the reasons of why we should give our method as an initial treatment.

Document from Nesbitt and Pharmacia & Upjohn company WO 02/053140 A2
The above document similarly to the Tollefson references (above documents) does not give any enablement of why to use the medication combination for the purpose of our claims and why and how the average artisan would be able to deviate from the current standard of care – without doing malpractice. There is no description or explanation of how the one skilled in the art could use the techniques of that document for the use of our claims, and contrary to the strong teaching against in the prior art. There is no risk benefit alternative analysis in that document either. That document therefore is not enabling for the purpose of our claims, and as we have shown we did apply new steps for our new use so there is novelty and inventive step that we have applied.

Document from Evins at al. (Am. J. Psychiatry 156:5, May 1999 pages 798-799.)
The opposing European attorney (not the patent office) alleges that the above reference of using buproprion (an accepted anti smoking medication that happens to be an antidepressant) together

with clozapine in schizophrenic patients (where the use of antipsychotic to target the hallucination and thought disorder is expected for that particular use) would make our method "obvious" even for non-psychotic patients. This logic is absurd and is not substantiated. Would the combination treatment for smoking cessation in non-psychotics be obvious that surprising result would have been commented on either by the authors or by the editorial staff.

Document from Ralph and Pfizer EP 1238676 A1.
The opposing European attorney (not the patent office) alleges that this prior art would take away the novelty for the purposes of at least some of our claims. However, we are submitting that the prior art is not enabling for the purpose of our claims, therefore the alleged prior art rejection proposed by the opposing European attorney should be withdrawn. The arguments are similar to the ones discussed under document from Tollefson and Eli Lilly company EP 0966967 A2; document from Tollefson and Eli Lilly company EP 0958824 A2; and document from Nesbitt and Pharmacia & Upjohn company WO 02/053140 A2.
The same applies as regards to the treatment of various substance abuses. Document 6 from Ralph and Pfizer is not enabling for that use (they only make a mere mentioning without reasons or explanations that would not allow the artisan to overcome the barriers and use it for the purposes of our claims). We on the other hand enabled our method through our description of the mechanism of action of the aforementioned class of medications on cognitive distortion and thus also for smoking cessation.
Even if (Ralph and Pfizer EP 1238676 A1) document would be enabled through one action (the substance abuse itself), that would not make another method acting on a different level (the cognitive distortion) unpatentable. (Just because gasoline is used to propel the engine of a car that does not mean that a hybrid car using electricity or hydrogen could not be patented).

(Further and similar reasons were also provided in our reply to the 1st and to this 2nd office action, that is exclusively referenced herein for the USPTO).

Hence we have shown that all of the allegations regarding prior art publications are only allegations from the (non-patent office) opposing European attorney.

Discussion in light of prior art of the new claims with atypical antipsychotic monotherapy, which claims are being introduced with information also being re-entered from the provisional application:

In our provisional application (claim 6) we have made reference to that the antipsychotic medication or a dopamine system stabilizer alone that is in monotherapy (and not just in combination with antidepressant) can also be used. A long discussion on enabling of how the antipsychotics would work in depression, reducing suicide, and targeting cognitive distortion also provided further support to that fact. (See also Appendix A of reply to 1st OA page 77-83. – parts re-entered from the provisional).

Many of our arguments in the reply to the 1st and 2nd OAs (e.g. risk/benefit analysis) would equally be applicable in defending against prior art as regards to the atypical antipsychotic monotherapy.

As regards to Tollefson 5,958,921 reference (Method for treating depression with olanzapine) the following should be noted:

1) While the claims of Tollefson make it clear that their intent was to claim treatment of patients "not diagnosed with a psychotic condition" (claims 1, 9, 12,) this particular application (the 5,958,921 reference) was not presented in a clear and unambiguous way to provide guidance, enablement, or even to know what particular patient population they were talking about. Their alleged enablement – as disclosed by Tollefson – is restricted of demonstration by clinical trial (page 4 5th paragraph on my printout from the PTO web page). There is nothing mentioned if these patients were MDD with TRD, bipolar depression (within the category of depression) or at times patients with schizophrenia or schizoaffective disorder showing depressive symptoms, (but right at the time of their assessment free of psychotic symptoms). If indeed Tollefson representing a major pharmaceutical company would have discovered a surprising new use (pre-requisite for an invention) for MDD, non-psychotic, non-TRD, – specifically with the number of patients referenced in his patent application being almost 2000, a publication in peer-reviewed clinical journals would have followed in ten years time. This applicant could not find anything of that nature. The corresponding publications were only for currently known use not conflicting with this applicant's claims. Therefore it is likely – and there is nothing to the contrary in Tollefson's patent application (the 5,958,921 reference), that the patients in the cited study of that patent application are a combination of MDD with TRD, schizophrenia (or schizoaffective disorder) with depression, and bipolar depression. The medical literature search corresponding to that patent application indeed reveals publications in these areas. It also has to be mentioned as revealed in our application, that both bipolar disorder and TRD are associated with high percentage of psychosis even if the psychosis often goes unrecognized. The language chosen by Tollefson of "a patient not diagnosed with psychotic condition" instead of using non-psychotic patient further reflects or supports that implication (i.e. that psychosis is not excluded, it is just not diagnosed). In addition, Tolefson reveals that olanzapine is useful for the treatment of mild anxiety – and the same was also known by prior art about antipsychotics in general. Although nothing was mentioned in this Tollefson reference about if depression with coexisting anxiety was or was not among their patient population, by either confirming or denying that fact, the targeted treatment of anxiety coexisting with depression could have contributed to their results if indeed such an undisclosed patient population would have been within their study. In summary, this particular application (the 5,958,921 reference) was not presented in a clear and unambiguous way to provide guidance, enablement, or even to know what particular patient population they were talking about. [See also 3) below.] Specifically, and in addition, no enablement was provided for MDD non-TRD, non-psychotic patients.

2) The PTO knows (e.g. as it was referenced to this applicant) that Tollefson (Eli Lilly) had study on MDD with TRD. We have also referenced in our application the Shelton study (2001 Am J Psychiatry) on TRD.

Now, it is a concern that the FDA has approved atypical antipsychotics – as monotherapy - for the treatment of bipolar disorder without specific warning that they may not be an equivalent alternative to the traditional mood stabilizers at least in subgroups of patients. It is known, that there is an overlap with psychosis in a high percentage of bipolar disorder patients:

> "About 2/3rd of patients with *bipolar (manic-depressive)* disorder are having a history of at least one psychotic symptom. Bipolar patients who are psychotic during one episode of affective illness are highly likely to be psychotic during subsequent episodes. [Tsai, SY. M., et al. 2002.])" (page 29 last four lines and page 30 1st line in our provisional application with size 14 copy –enclosed).

Therefore, in bipolar disorder the antipsychotic monotherapy targeting psychosis, agitation, and anxiety may show a significant difference in the improvement of patients but only as for the group. That does not mean that the atypical antipsychotics can replace the traditional mood stabilizers for all subgroups (and in non-psychotic bipolar patients). Unfortunately the FDA and the clinical marketing did not draw attention to that potentially and likely misleading link. At least a subgroup of the bipolar patients who are withheld from the benefit of the traditional mood stabilizers may suffer, as the above fact/concerns were not mentioned or emphasized by the FDA. The same may be true for the treatment of TRD. As we noted in our provisional application (page 35 last 3 lines and page 36 lines 3-4):

> "It had been estimated that a significant proportion, 15% of major depressive episodes fulfill the criteria for psychotic subtype. (Gumnick, J.F. et al. 2000). ...
> ...Nierenberg had noted that in many cases, the cause of treatment-resistant depression may be an unrecognized psychosis. (Nierenberg. A. A., 1992)."

The Shelton study referenced in our application (2001 Am J Psychiatry) did show only a modest improvement with olanzapine monotherapy for the treatment of TRD, but as is known in a significant percentage of TRD the cause may be the unrecognized psychosis. That may explain the overall difference, and also of why there was only for modest effect for the olanzapine monotherapy for TRD.

We provided enablement in non-TRD through various different mechanisms (as revealed in the reasons part) and also on the interaction of medications, psychological and [gene expression effect].

The Shelton, the Tolefson (5,958,921 reference) or similar studies on TRD therefore cannot be extrapolated without enablement to non-TRD.

3) Tollefson also disclosed studies on the effect of olanzapine on "anxious and depressive symptoms accompanying schizophrenia". (Tollefson GD et al A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998; 43: 803-810.) In that study, Tollefson specifically stated that "anxiety and or depression may persist in the absence of overt psychosis" [in the schizophrenic patients]. (page 806 second column under discussion, line 5-7). Whether their patients disclosed in their study referred to in their 5,958,921 application as "not diagnosed with psychosis" included that patient population is unknown, thus the 5,958,921 reference was not presented in a clear and unambiguous way.

4) In the 5,958,921 reference Tollefson refers to their international double-blind study involving almost 2000 subjects randomized to receiving either olanzapine or haloperidol for 6 weeks. It is respectfully submitted that

a) in order to conduct such a large scale study usually smaller non-double blind study is conducted and revealed. (We have not found such a study in the literature for MDD non-TRD, non-psychotic).

b) It had been known in the literature (as it was also disclosed by the applicant) that haloperidol can cause depression. In fact Tollefson was also revealing that finding.

c) With all that and with the knowledge of the art at the time of Tollefson's application it is respectfully submitted that no ethics (research) committee would have approved such a large scale study on unipolar depression, MDD with non-psychotic and non-TRD, and from the definition of unipolar depression on non-bipolar patients.

d) In addition claiming an antidepressant effect (for non-psychotic patients) in comparison to a drug that is known to cause depression is a non-convincing rational.

e) As regards to patients with schizophrenia Tollefson has revealed that "the literature generally reflects that given an adequate dose and time interval for a positive symptom response to conventional antipsychotic drugs, some mood improvement will be seen". Pages 806 second column under discussion lines 18-21. (Tollefson GD et al A double-blind, controlled comparison of the novel antipsychotic olanzapine versus haloperidol or placebo on anxious and depressive symptoms accompanying schizophrenia. Biol Psychiatry 1998; 43: 803-810.) Therefore no generalization can be made of the "antidepressant" effect of antipsychotics for MDD non-TRD, non-psychotic patients.

5) In the 5,958,921 reference Tollefson makes mention of his intention of using the term "treating" including profilaxis, but no enablement for how that would be achieved, or proven by clinical trials were presented.

In summary, the 5,958,921 Tollefson reference is not a clear and unambiguous disclosure and evidence presented for enablement as regards to our invention.

Additional remarks

The applicant feels that his invention has a great importance to solve a long felt need, and of saving lives. In fact it could have been saved up till now up to almost half of the fatalities of the worst (contagious) infectious epidemics of all times in the USA (the fatalities of the 1918 flu).
The applicant has attempted to convince a large pharmaceutical company on a confidential basis to pay attention to this topic and conduct studies, receiving only opposition from that drug company. The applicant felt that providing an incentive to the pharmaceutical industry through a patent application may help moving this issue to the right direction. So far the applicant was only disappointed on the relative lack of interest and the absolute lack of action.

Claims discussion:

Summary of the reply to the Claim Objections

Replies # 8-9 and Reply C should sufficiently address the withdrawal of claims 59, 60-62, 98-103, and 109-118 objected under 37 CFR 1.75 as being a substantial duplicate thereof of claim 1 or 2. We have shown that it does not cover the same thing. These involve additional steps so they are not **various motivations** for the treatment such as, "for resisting suicide," or, "for the benefit of the group of patients." They also materially alter the patient population, as it brings the method to the "first choice of treatment" and changes "the standard of care" (which terms are definitions used in the art). Therefore MPEP § 706.03(k) cannot apply as it was used herein. Moreover claims 109-118 don't have the initial treatment limitation (therefore are not duplicate of claims 1 or 2).

Replies # 6, #16-19, and Reply D should sufficiently address the withdrawal of maintained claim ***Rejections - 35 USC 5 112*** first paragraph on **enabling for** Claims 1-15, 36-38,41-43, 48-74, 95-106, and 1 09-1 18 not only **for a method of treating depression, cognitive distortions, smoking cessation, or nicotine withdrawal** comprising administering certain antidepressants defined in the specification that was already acknowledged as enabling, but also for **enablement for such a method involving the described class of antidepressant and antipsychotics.**

Claims 1-3 were amended. The issue of cognitive distortion was addressed starting at page 5.

Replies #16-17, #6, and Reply F should sufficiently address the withdrawal of rejections described by the PTO at Page 10 as our under reply #16 has addressed that the applicant's theory and enablement was relevant and for the ordinaly skilled in the art sufficient to practice the invention (therefore the enablement requirement was met), and replies #6 and #17 addressed the issue of the **functional language** raised above. Therefore objections should be withdrawn for clams 1-3 as for the described classes of medications.

Claims 1-3 were amended. The issue of cognitive distortion was addressed starting at page 5.

The same Replies #16-17, #6, and Reply F & I should sufficiently address the withdrawal of rejections with regards to With regards to "new" claims 55-118, that was addressed by the PTO at Page 12.

Replies J, Q (q) & R should sufficiently address the withdrawal **new grounds of rejections** (raised at page 12 - 13) (***Claim Rejections - 35 USC 5 112*** second paragraph as being indefinite, since specific instructions had been given in the utility in describing the meaning of the "low dose". This is particularly true for typical antipsychotics where "chlorpromazine equivalent" doses were commonly used.

Reply #9 & Reply K and should sufficiently address the withdrawal new grounds of rejections (page 13) for Claims 55, 57, 60, and 63-108 that recite the limitation "treating substantially all patients treated by said physician", claims 55, 57, would be amended as: ... substantially all of said patients...

55. (Amended):

57. (Amended):

Thus these claims would have sufficient antecedent basis for this limitation in the base claims 1 and 2 without new limitations introduced.

Reply #10 & Reply L should sufficiently address the withdrawal new grounds of rejections (page 14) for Claim 65 is rejected under 35 U.S.C. 112, first paragraph, as it is not failing to comply with the written description requirement and not deemed to insert new mater, since the active metabolite of risperidone is inherent just like as in our analogy of grape the grape juice would as when it is eaten it is grounded with our teeth (and metabolized).

Reply #9 & Replies K & M should sufficiently address the withdrawal new grounds of rejections (page 14) for Claims 55, 57, 60, and 63-108 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the

written description requirement deemed to insert new mater, as Claims 55, 57were amended as above with substantially all of said patients therefore these claims would have sufficient antecedent basis for this limitation in the base claims 1 and 2 without new limitations introduced.

For the same reasons (on page 15) the enablement requirement rejection for these claims should be withdrawn as Reply #9 & Replies K & M should sufficiently address that along with the other arguments.

Replies #8-9 # & Reply O should sufficiently address the withdrawal of rejections (page 19) for Claims 43, 98, 109, 110 rejected under 35 U.S.C. 112, first paragraph, **(enabling) since the wording of these claims will be amended from preventing to resisting:**

43. (Currently amended):
98. (Currently amended):
109. (Currently amended):
110. (Currently amended):

Replies # 8-9 and Reply C should have sufficiently addressed that resisting is used not just for **various motivations but** involve additional steps like risk benefit analysis, and introduces a new method to the art that saves lives, relives suffering and helps patients. These are just as invaluable as any new medical treatment methods.
The PTO already acknowledged that these claims already **enabling for a method of treating depression and associated conditions, and avoiding, protecting against, or remedying relapse or recurrence of depression.**

Replies #1-5, Figures 1-2 & Replies Q (q) & O should sufficiently address the withdrawal of obviousness rejections (pages 25-26) (***Claim Rejections - 35 USC 103(a)*** for Claims 1-6, 9, 1 1, 13, 14, 16-1 8, 20-22, 24-26, 28-30, 32-37, 41-43,48,49, 51, 53, 54-68, 70, 72, 73, 75-77, 79-81, 83-85, 87-89, 91 -104, and 109-118 that were rejected as being unpatentable over Tollefson. There is along line of argument, but there is a repeated pattern by the PTO examiners of conditioning their reasoning, while these exact conditions are not meeting the reality checks. **For example the PTO's line of reasoning is deviating so much from the standard of care that would lead to malpractice.** If the PTO's reason of "because" that is conditioning is false that makes the entire PTO statement, and the conclusions - including the basis of the claim rejections also false!

In addition to Replies #1-5, Figures 1-2 & Replies Q (q) & O that should sufficiently address the withdrawal of obviousness rejections (page 30) (***Claim Rejections - 35 USC 103(a)*** for Claims 8, 19, 23, 27, 31, 78, 82, 86, and 90 as being unpatentable over Tollefson in view of Kelleher that was sufficiently addressed in Reply S discussing aripiprazole.

Pages 6-15, Reply #3, pages 6-15, Figure 2, (and in broader sense Replies #1-5, & Replies #8-9) as well as Replies T & U should sufficiently address the withdrawal of obviousness rejections (page 31) for Claims 1-2,4-6, 9-11, 13-1 4, 37-38,42,48, 51, 53-64, 66, 69, 70, 73, 96-104, and 109-118, as being obvious over Faour. The PTO had ignored our reply to the 1st office action and the PTO showed an unconvincing line of reasoning.

Reply #4, Figure 2, (and in broader sense Replies #1-5, & Replies #8-9) as well as Replies V & W should sufficiently address the withdrawal of obviousness rejections (page33) for Claims 1-2, 4, 7, 9, 11-15, 37, 38, 42, 48, 51-62, 70-74, 96-105, and 109-118 are rejected under 35 U.S.C. 103(a) as being obvious over Chappell. There is a long line of argument, but there is a repeated pattern by the PTO of conditioning their reasoning, while these exact conditions are not meeting the reality checks. For example the PTO's line of reasoning is deviating so much from the standard of care that would lead to malpractice. If the PTO's reason of

"because" that is conditioning is false that makes the entire PTO statement, and the conclusions - including the basis of the claim rejections also false!

In addition to Reply #4, Figure 2, (and in broader sense Replies #1-5, & Replies #8-9) as well as Replies V & W should sufficiently address the withdrawal of obviousness rejections (page33) for the above mentioned Claims rejected under 35 U.S.C. 103(a) as being obvious over Chappell, and **Reply X** should sufficiently address the withdrawal of rejections for Claims 106-108 are rejected under 35 U.S.C. 103(a) as being unpatentable over Chappell in view of Berman simply because of disclosing that ketamine exerts antidepressant effects in clinical research experiment. Clinical reasoning were given in Reply X of why the PTO's line of argument was not convincing.

It is important to note that suicide takes about 30.000 lives in the US alone resembling the death rate from leukemia. In five years it is up to 150.000 lives in the US alone that could have been saved – which is almost about half of the fatality of the worst (contagious) infectious epidemic in the US ever (the 1918 flu epidemic) – even though the effectiveness of our method may not be 100%. The PTO cannot assume that if our invention would have been obvious in light of the prior art than the secondary factors would so drastically contradict to the PTO's assumption 5 years later. In discussing the secondary factors in the 1st reply we also made reference of the potential and likely legal liabilities form "big pharma" and the FDA of not coming forward to the media with such an important discovery. We also mentioned the financial incentives for "big pharma" in the range of billion(s) of dollars a year. The PTO did not address our arguments about the secondary factor, and did not even acknowledge the existence of that section.

We respectfully request the allowance of our amended claims.